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Individual Variability of Functional Connectivity in Resting-State and Naturalistic fMRI Paradigms

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Abstract

Resting-state functional magnetic resonance imaging (fMRI) studies are criticized for their lack of control over cognitive states of individuals during observation, which may lead to increased variability in estimates of functional connectivity (FC). Engaging movies have been used in an attempt to synchronize the cognitive states of individuals during the scan, potentially reducing intersubject variability in connectivity estimates. The objective of this study was to investigate the differences in intersubject variability of FC between rest and movie conditions in a healthy cohort. The results demonstrate widespread reductions of intersubject variability of FC in the movie condition compared to the resting-state condition. These differences were pronounced in regions of the frontal, auditory, and visual cortex, suggesting effects on sensory areas as well as areas responsible for higher-order functioning. Because of its potential as a biomarker, less variable normative estimates of FC are beneficial for developing more sensitive tests for clinical use.

Keywords: fMRI, Naturalistic Stimulation, Resting-State, Variability

Summary for Lay Audience

Functional magnetic resonance imaging (fMRI) is a technique used to measure brain activity. Activity can be measured in response to a task or when the subject is in a resting state, that is, when there is no direct stimulus applied. Resting-state scanning is typically performed to investigate the interregional relationships between spatially disparate areas of the brain, that identify networks of regions which appear to be working together. The dysregulation of these networks has been implicated in certain disease states, such as Alzheimer's, depression, and schizophrenia. This provides an opportunity for functional connectivity to potentially be used as a diagnostic or prognostic tool for these diseases. However, these tests have yet to be applied in the clinic due to a lack of sensitivity in detecting disease states.

A possible explanation for its lack of clinical success may be the absence of behavioural constraints placed on subjects in resting-state scanning, allowing them to drift into a variety of different states of mind. These states are likely inconsistent across subjects during the scan and can therefore cause increases in variability of the measures. Increased variability may cause the networks in healthy people to look more different than they are, making it difficult to identify features separating them from individuals with disease.

However, a recently popularized technique has attempted to use movies to synchronize the states of individuals during the scan. Using movies, researchers have shown that brain activity is synchronized across subjects based on the time locked events of the movie. In this study, we investigated the effects of movie watching on variability of the interregional relationships, known as functional connectivity, and compared it to what is observed in the resting state. We hypothesized that movie watching would result in less variable networks across individuals than the resting state because of the mental constraints placed upon individuals during movie-watching.

The results of the study demonstrated that movie-watching led to less variable functional connectivity compared to resting-state scanning. Future work is needed to investigate whether the reductions in variability lead to more sensitive tests for clinical abnormalities.

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List of Abbreviations

BOLD Blood-Oxygen-Level-Dependent

dFC Dynamic Functional Connectivity

DMN Default Mode Network

EEG Electroencephalography

EPI Echo Planar Imaging

FC Functional Connectivity

fMRI Functional Magnetic Resonance Imaging

GLM Generalized Linear Model

HCP Human Connectome Project

ICA Independent Component Analysis

ISC Intersubject Correlation

ISFC Intersubject Functional Connectivity

MRI Magnetic Resonance Imaging

PET Positron-Emission Tomography

ROI Region of Interest

Chapter 1

Introduction

1.1 Motivation

Resting-state functional magnetic resonance imaging (fMRI) has been studied extensively for the past two decades. It has facilitated a number of discoveries related to brain function in the absence of external stimulation and has broadened our understanding of functional brain organization. Metrics derived from the study of subjects in resting-state have even shown promise as potential biomarkers because of their relative stability over time. However, the resting-state paradigm has faced criticism throughout its existence, predominantly because of its limited control over the cognitive states of individuals during the scan [1]. With no behavioural constraints applied during the scan, the only interpretations that can be conclusively made from results in resting-state studies are based on physiology, with cognitive results being mostly speculative. Despite the criticism, no techniques up to this point have been as widely adopted to assess global functional connectivity as the resting-state paradigm.

A recently developed paradigm has attempted to use movies to synchronize the cognitive states of individuals during scans, but little work has been done to investigate its effects on metrics of connectivity. This thesis will examine the history of the resting-state paradigm, its relation to the functional organization of the brain, and discuss a possible alternative to resting-state in the movie watching paradigm. This will include a review on the potential improvements in sensitivity to abnormalities of connectivity provided by the movie paradigm, and its utility as

a clinical tool. Specifically, the second part of this thesis will address whether movie watching results in reduced intersubject variability of functional brain organization when compared to resting-state fMRI.

1.2 Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) allows researchers and clinicians to obtain high resolution images of soft tissue without exposing an individual to ionizing radiation. The human body is made up primarily of fat and water, which contain hydrogen atoms, and MRI makes use of the nuclear magnetic resonance signal from hydrogen nuclei. When a strong magnetic field is applied, the net magnetization of the protons will precess about the direction of the applied magnetic field at a specific frequency, known as the Larmor frequency [2]. The Larmor frequency is dependent on the gyromagnetic ratio of the particle as well as the strength of the applied magnetic field [2]. Additional smaller magnetic field gradients are also applied in orthogonal directions which change the Larmor frequency of protons as a function of their position in the space of the scanner, allowing for specificity in determining the locations of signal origin [3]. By applying a radio frequency pulse at the Larmor frequency of a particular region, the net magnetization can be rotated away from the direction of the applied magnetic field [4]. While the net magnetization is directed away from the direction of the applied magnetic field, the protons emit radio frequency energy that is recorded [5]. The emitted radio frequency energy is strongest when magnetization vectors of smaller regions are in phase with one another. However, over time the vectors dephase because of molecular interactions and magnetic field inhomogeneities, and the net magnetization vectors return to the direction of the applied magnetic field [6]. The dephasing of magnetization vectors and restoration to the applied magnetic field are known as relaxation processes [6]. T1 relaxation, known as spin-lattice relaxation, is the process by which the net magnetization returns to its equilibrium value in the direction of

the applied magnetic field [6]. T2 relaxation, known as spin-spin relaxation, is the dephasing of magnetization vectors because of differences in Larmor frequencies [6]. T2 relaxation can be caused by molecular interactions or inhomogeneities in the magnetic field, and the combined effect of the possible T2 types is known as the T2* relaxation [7]. The signal obtained in MRI is based on the length of these relaxation times, in that longer relaxations result in stronger signals. Because of this, contrast can be achieved by taking advantage of differences in relaxation times between different tissue types.

Functional MRI is a powerful technique that provides an indirect measure of neuronal activity through a blood oxygenation level-dependent (BOLD) contrast. The BOLD contrast is based on the concept that neural activity in the brain causes increased metabolic demand, resulting in a vasodilation of the vessels that supply oxygen to the active region [8]. However, the blood flow into the region significantly overshoots the oxygen metabolism requirements, leading to an increase in the ratio of oxygenated blood (i.e. oxyhemoglobin) to deoxygenated blood (i.e. deoxyhemoglobin) [8]. Because deoxyhemoglobin is strongly paramagnetic, it causes distortions in the magnetic field which contribute to a faster T2* relaxation time [9]. Therefore, when the vessels in a region contain a higher ratio of oxyhemoglobin - which is only weakly diamagnetic – to deoxyhemoglobin, the T2* relaxation time increases leading to a larger signal emission from that region [9]. Through studies performed on sensory cortices of lower mammals, it has been shown that the BOLD signal is highly correlated with the underlying local field potential [10, 11]. The local field potential is primarily composed of the summation of the inhibitory and excitatory postsynaptic potentials and therefore represents input signal to a brain region rather than output [2]. The coupling of local field potentials with the BOLD signal is the basis of its use as a proxy measure of neural activity.

A typical high-resolution anatomical MRI scan with a voxel size of less than 1mm isotropic can take approximately 5-10 minutes to acquire. In functional imaging, the images must be acquired at a much faster time scale to accurately capture the fluctuating activity occurring in response to a task paradigm or at rest. To achieve this, an acquisition mode known as echo pla-

nar imaging (EPI) is typically used which implements rapid magnetic field gradient changes to acquire the entire image with one radio frequency pulse [12]. While this allows for a sampling rate between 1-3 seconds, it comes at the cost of spatial resolution. Typical anatomical MRI scans are acquired at a voxel size of $0.5mm^3$, whereas functional scans are typically acquired at a voxel size of $2mm^3$, meaning the voxel size of the functional scans is larger than the anatomical scans by a factor of 64. Beyond diminished spatial resolution, EPI faces challenges at higher magnetic field strengths. Susceptibility differences, which lead to magnetic field inhomogeneities, are proportional to the strength of the magnetic field [13]. This means that as magnetic field strengths get higher, signal loss and geometric distortions in T2* weighted imaging can become particularly pronounced [13]. Ultra-high magnetic fields strengths also shorten the length of T2* relaxation which can result in signal loss when using traditional imaging techniques [13]. To compensate for this, parallel imaging techniques can be used to mitigate the effects of shortened T2* and accelerate acquisition [13]. Nonetheless, fMRI provides localization of functional activity in humans at a much higher spatial resolution than that which can be achieved using noninvasive electrophysiological methods such as electroencephalography (EEG).

Although this brief overview is an oversimplification of the physics underlying MRI and the biological underpinnings of the BOLD signal, an understanding of the basic concepts of the technique is important for appreciating the interpretations that can be made from results of fMRI studies such as the one presented in this thesis. There are a variety of limitations and possible confounding effects involved in the acquisition of the BOLD signal, however it remains one of the most popular measurement tools in the field of neuroscience.

1.3 Resting State

1.3.1 Introduction

The resting state is traditionally described as a condition in which there is no imposed stimulus on the experimental subject. In most studies utilizing the resting-state paradigm, the subject is told to simply lay in the scanner and think about nothing in particular. In the first three years of fMRI, studies focused solely on isolating activity patterns in response to stimuli from task-based experimental designs. These studies typically made use of mass univariate statistical methods to attribute functionality to localized regions by looking at task-dependent signal changes [14]. Signals beyond those related to the task paradigm were labeled simply as noise and not given any consideration in the analysis stage. This assumed that the only meaningful signal that could be observed was that which was measured in response to the participant's engagement in a task. However, in 1995 a seminal study from Bharat Biswal and colleagues observed that during the rest portions of his motor experiment, homologous sensorimotor regions in opposite contralateral hemispheres showed correlated low frequency activity. This demonstrated for the first time that meaningful conclusions could be found in signal from regions which were not being explicitly targeted with a task [15]. Biswal observed that during the rest portions of his motor experiment, homologous sensorimotor regions in opposite contralateral hemispheres showed correlated low frequency activity. Although the strength of the correlation in brain activity was not as strong as was seen in the motor task, the observation of structured activity during rest between two regions at all was surprising. This study suggested that, even when not engaged in an active task, the brain maintained coordinated neural activity between regions with related functionality. Although the neuroscience community was slow to accept this idea into mainstream thought, it was echoing ideas that had been discussed for decades [16].

Physiologists as far back as 1914 have hypothesized the existence of meaningful endogenous neural activity, including Thomas Graham Brown who believed that a large part of the

brain's function was intrinsic and involved the acquisition and maintenance of information to develop an accurate understanding of the external environment [16, 17]. However, because Biswal's findings came when fMRI was only a few years old, the BOLD signal was not yet well characterized so the neuroscience community was cautious to label the result as functionally relevant rather than as a product of noise in the data [18]. Much of the work within the first years after [15] was devoted to determining whether the low-frequency fluctuations were neurally driven, or were noise. Biswal followed up his original study with one demonstrating that the effects were diminished under hypercapnia conditions and returned to normal upon re-establishment of regular air breathing [19]. He also demonstrated that the effects were present when using a direct measure of blood flow, which can be done with arterial spin labelling [20]. What finally caught the attention of the broader community was the PET study from Marcus Raichle and colleagues which demonstrated that there was a group of interacting brain regions that become more active when the subject was not performing a task [21]. Following up on Raichle's findings, Michael Greicius and colleagues showed that the regions which had been found to activate during rest also demonstrated high correlations with each other in resting-state fMRI [22]. Together these studies helped establish resting-state fMRI as a functionally relevant paradigm and allowed it to gain acceptance in the field of neuroscience.

1.3.2 Functional Connectivity

Once it was established that the low-frequency correlation findings of Biswal did have functional relevance, the field of resting-state fMRI took off. The study of those correlational relationships is now referred to as the study of whole-brain functional connectivity, and a number of different analysis techniques have been proposed to capture these relationships. The two most popular techniques are seed-based analysis, and independent component analysis (ICA). Seed-based analysis involves the selection of a region of interest (ROI), which could be a single voxel, or a group of functionally similar voxels averaged together, and calculating the Pearson

correlation between that ROI's time series and the time series of every other voxel/region in the brain. This provides a spatial map showing the strength of connectivity between that ROI and the rest of the brain (Figure 1.1).

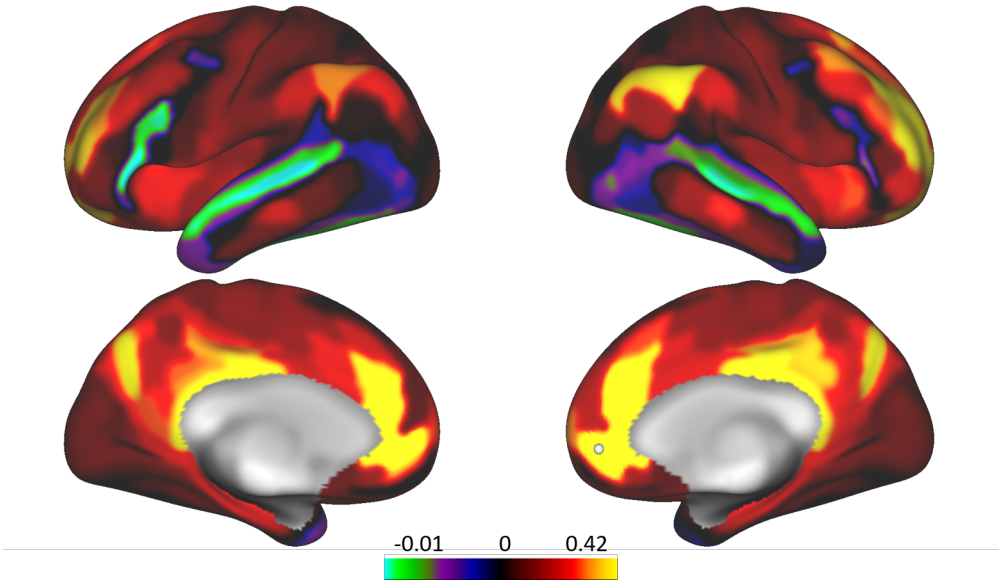

Figure 1.1: Example functional connectivity map with seed placed in ventral medial prefrontal cortex

This analysis can be performed for every voxel or region in the brain to generate a functional connectivity matrix which shows the strength of correlation between every pair of ROIs (Figure 1.2). While this method is relatively simple, it can be computationally demanding, and the results can be difficult to interpret. Another popular approach is ICA, a method that separates the data into a set of additive components based on maximal statistical independence. In resting-state fMRI data, ICA can identify spatial networks comprised of weighted sets of voxels that share a common network time series [23]. Although this technique is more efficient and makes results easier to interpret, it generally results in the same conclusions as the seed-based analysis when examining a group of healthy subjects [24].

Today, it is understood that the brain has intrinsic patterns of connectivity which are consistently observable across multiple task conditions as well as in the resting state [25]. These patterns of connectivity form networks which have been named for hypothesized functional re-

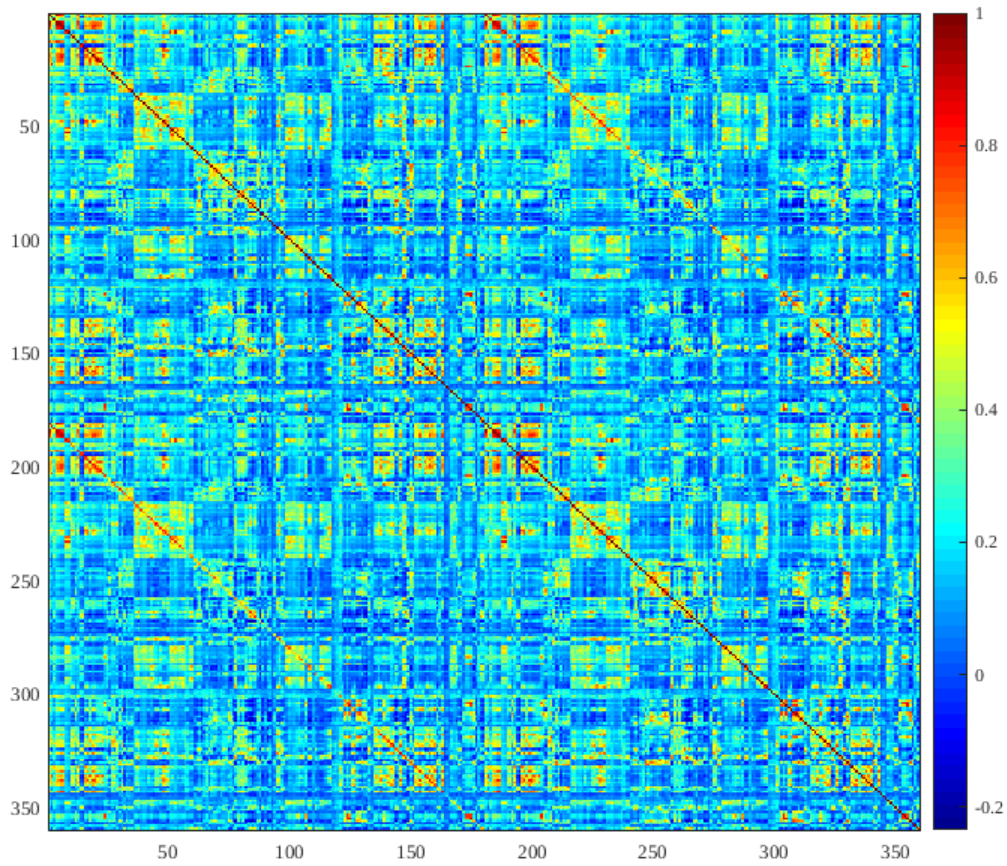

Figure 1.2: Example functional connectivity matrix. The x and y axes are identical and show the indices of regions being analyzed. The colour bar on the right of the figure shows the strength of correlation between any two regions.

sponsibility based on activation studies. The canonical networks, which can be seen in Figure 1.3, include the default mode, the visual, the somatomotor, the language, the ventral attention, the dorsal attention, and the frontoparietal networks. Typically, these networks are described as either task-negative networks, which appear to be more active at rest, or task-positive networks, which are more active when an individual is engaged in a task [26]. In functional connectivity analyses, these changes in activation manifest themselves through increases in correlation strength between pairs of ROIs within the network during the task [27, 28]. Although the strength of the connections may be altered by condition-specific demands, the to-

pography of the network structures is commonly shown to be fairly stable in both rest and task states [29, 30], suggesting that the network structure is driven at least in part by a physiological process rather than by cognitive function alone.

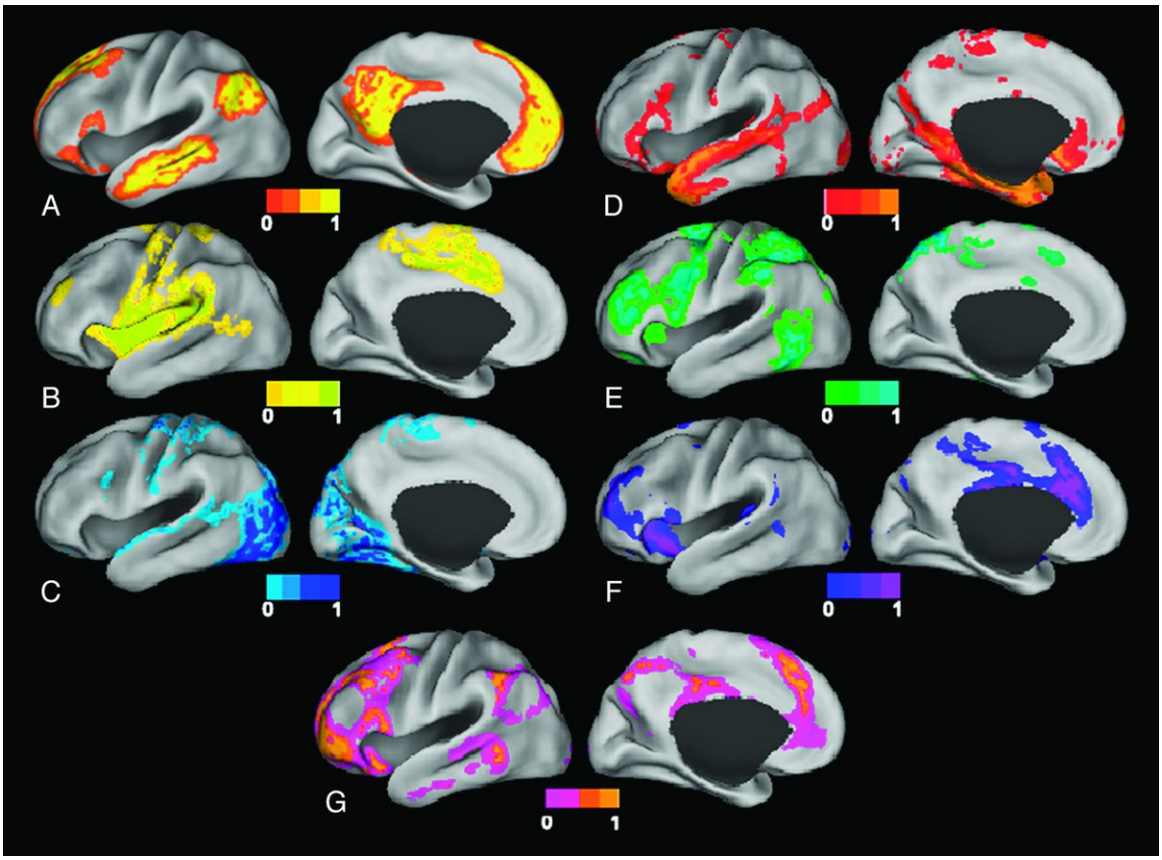

Figure 1.3: Canonical Resting-State Networks: A - Default Mode Network, B - Somatomotor Network, C - Visual Network, D - Language Network, E - Dorsal Attention Network, F - Ventral Attention Network, G - Frontoparietal Control Network. [25]

The consistency of network structure in the resting-state paradigm may contribute to the efficient and reliable estimates of group functional connectivity. It has generally been found that, in healthy subjects, the group connectivity estimates in resting-state fMRI stabilize after approximately 5-7 minutes of scan time [31]. The effects of spurious connections can be further reduced by performing longer scans; however the benefits of increases in scan length beyond the 10-minute mark have been shown to be relatively minor [32]. Investigations into the effects of scan length on group connectivity estimates have found that the longer the duration of the scan, the more the connectivity estimates mirror the anatomical connections between regions

[33]. This suggests that the most stable connections in group estimates may exist because of a dependence on common anatomical connectivity. The consistency of these networks has led many researchers to use functional connectivity as a stable trait-like measure, with studies linking it to individual differences in behavioural or cognitive measures [34].

Despite the stability of mean functional connectivity estimates at the group level, the variability around the mean may be high, and may differ across the brain. The spatial distribution of individual variability in functional connectivity has been explored in the resting-state paradigm. In a study of 25 healthy subjects, Mueller and colleagues obtained five six-minute resting-state scans across six months to estimate variability of functional connectivity across subjects while controlling for within-subject variability. They observed that the highest levels of intersubject variability occurred in heteromodal association cortex, and the lowest levels of variability occurred in unimodal primary sensory cortex [35]. The authors suggest three explanations for their findings. They believe that the differences in variability may be explained by the prolonged maturation of association cortex, which shows the most pronounced post-natal cortical expansion [36], involving extended exposure to extrinsic and variable experiences during a time of high neuroplasticity [37]. Following this, their second rationale is that the structure of cortical areas with protracted maturation is less susceptible to genetic influences, allowing for a greater environmental influence [38]. Finally, they argue that synaptic overproduction, which is highest in prefrontal cortex and lowest in primary sensory regions [39], may allow for greater freedom in activity and environment dependent synaptic pruning during development. However, the authors do not comment on the effects that divergent cognitive states during scanning may have on functional connectivity estimates.

There is evidence to suggest that functional connectivity estimates can be altered with changing cognitive state and cognitive demands [40, 41]. Indeed the study of psycholphysiological interactions in task-based fMRI studies have shown for two decades that altered cognitive states have focal effects on certain connections depending on the task paradigm [42, 43]. Recent work has argued that functional connectivity contains both stable trait-like aspects as

well as more transient aspects which can be attributed to an individual's cognitive state and environment. In a 2015 study, Geerligs and colleagues demonstrated that the degree of similarity of functional connectivity across a group of subjects was higher in a sensorimotor task than at rest, suggesting that individual task paradigms may restrict the variety of cognitive states being sampled [44]. The concept of free-flowing cognition during resting-state scanning has been explored by calculating dynamic functional connectivity (dFC). In dFC, functional connectivity is analyzed on the scale of seconds to minutes in an attempt to capture changes in connectivity over time, which may reflect various cognitive states that individuals move into and out of over the scan duration. Despite controversial opinions surrounding the technique, dFC studies using resting-state fMRI data have shown that distinct and repeatable patterns of functional connectivity emerge which differ from the average connectivity observed over long time scales [45]. DFC has suggested that networks that were previously believed to be stable may actually demonstrate flexibility and modularity on shorter time scales.

To investigate how changing cognitive states may drive individual differences in functional connectivity architecture, previous work has probed the self-generated thoughts of individuals during resting-state scanning through questionnaires [46, 47]. These studies have shown that general patterns of thought were related to changes in an individual's functional architecture. For example, individuals who reported more imagery in their thoughts during the scan showed larger low-frequency fluctuations (a measure of resting-state activity) in the perigenual cingulate cortex, an area linked to the default mode network [47]. Another study demonstrated a positive correlation between proportion of visual thought and strength of functional connectivity in medial visual and occipital visual areas [48]. Although it has not been well established how uncontrolled cognitive states affect functional connectivity, it is important to be aware of the impact that free thought may have on estimates of functional connectivity.

Although general patterns of functional connectivity have been demonstrated in group resting-state studies with long scan durations, recent work has challenged the idea of a rigid functional architecture. Dynamic functional connectivity and task-based functional connec-

tivity studies suggest that the brain's functional networks are more flexible than previously thought, and that the structure of these networks change based on an individual's cognitive state and external environment.

1.3.3 Applications

Beyond the use of resting-state fMRI as a research tool, it has also been investigated for potential clinical applications, with the majority of work focusing on its use as a biomarker. In any clinical application, the resting-state paradigm has significant advantages over task-based paradigms. Some tasks can be difficult for clinical and pediatric patients to perform properly, so the resting-state paradigm allows us to work around the confounds that a complex task can introduce by requiring no action at all [49]. Task-based fMRI is also only designed to activate a small subset of regions while the resting-state paradigm allows for a global sampling of brain activity, reducing the scan time needed when information about multiple networks is required [25].

Because of its stability over long scanning times, many believe that functional connectivity could be used as a biomarker [50]. Biomarkers are measurable physiological indicators of a disease state, that provide objective diagnostic and prognostic criteria. The earliest successful investigations into clinical differences in functional connectivity focused on Alzheimer's disease; such studies have repeatedly demonstrated reduced connectivity in the default-mode network. This finding appears valid as the default-mode network is linked to episodic memory retrieval, and Alzheimer's disease is associated with disrupted episodic memory [51]. In studies of functional connectivity differences in depression, increased connectivity in the default-mode network (DMN) has been observed as well as reduced connectivity in the salience network, which is linked to monitoring and generating autonomic responses to salient stimuli [52, 53]. These findings suggest that non-invasive fMRI may be able to detect indications of disease earlier than traditional diagnostic techniques. Less success has been had in other disorders such

as schizophrenia and ADHD, but the study of these clinical differences is still fairly new, with novel methods of analysis constantly emerging which could prove beneficial for identification of meaningful differences. Although the early success in this domain has been promising, the resting-state paradigm may not be ideal for detecting biomarkers related to functional connectivity. The reasons for this are discussed in the next section.

1.3.4 Limitations

Despite the promise of the resting-state paradigm, its use as a distinct state to be studied has been criticized. Because of the unconstrained nature of the paradigm, there is skepticism surrounding the conclusions that can be drawn from studying the resting state. The first major criticism, which was outlined in a review by Morcom and Fletcher, is that the resting-state may not represent a baseline cognitive or physiological state as many researchers claim [1]. A popular belief among resting-state researchers is that it involves an individual's transition to a "default mode" with most regional activity representing a baseline level that has developed through a habitual recurrence of this state [21]. Morcom and Fletcher argue that the resting state should have no such status, particularly in relation to cognition, because the processes engaged at rest are largely unknown. If the cognitive processes occurring at rest are not clear than it is difficult to know which regions are truly in a baseline state and which are being recruited for some unobservable 'task'. Investigations which have probed mind-wandering content during resting-state scans through self-report surveys have shown that there may be multiple dimensions of cognitive processing that can occur during a scan [54]. However, it has been shown that the oxygen extraction fraction (OEF), a measure of the ratio between oxygen delivery and consumption, is roughly uniform across the brain at rest [21]. Morcom and Fletcher acknowledge that this may indicate a form a physiological baseline but question its relevance to investigations of cognition.

The opinions of Morcom and Fletcher [1] largely concern the use of resting-state in studies

related to cognition. They accept that the paradigm may have applications in methodological development and may potentially be of diagnostic or prognostic value. However, the paradigm still faces challenges in these contexts for three reasons. The first reason concerns the previously mentioned domains of cognition which may occur when an individual is at rest. Because individual differences in these processes have been shown to affect estimates of functional connectivity, the variability of mind-wandering during the scan may introduce clinically irrelevant variability to estimates. One would expect that clinical differences in functional connectivity would remain constant while differences in content of mind-wandering would be dynamic and reduce the sensitivity to true differences (which might be identifiable in a more constrained state).

The second reason concerns the tendency for individuals to fall asleep during the scan. The absence of explicit task demands and external stimulus, beyond earplug-dampened MRI scanner noise, leads to a monotonous environment which promotes fatigue and can lead to large and variable changes in wakefulness of the subject [55]. Research using combined EEG-fMRI have assessed wakefulness during scanning and the effects of varying levels of wakefulness on functional connectivity. One previous study found that over 50% of individuals fell asleep during the scan, and that significant differences in functional connectivity could be observed based on the sleep stage observed [56]. This introduces a major limitation for the establishment of FC abnormalities as biomarkers, as the differences observed may be caused by variable states of arousal. This is particularly concerning in relation to disorders which cause changes in alertness and wakefulness, such as Parkinson's disease and multiple sclerosis [57]. The influence of differences in arousal may lead to false positives or false negatives of FC abnormality, introducing unreliability and reducing its efficacy as a diagnostic tool. It has even been suggested that the failure of functional connectivity as a clinical tool may be explained by heterogeneous brain states associated with fluctuating wakefulness [56].

The final important concern with the resting-state paradigm is related to head motion during the scan. In task-based studies, head motion is less of an issue because the motion is generally

not related to the experimental paradigm, so its effects can be suppressed through averaging over many trials. However, the lack of an experimental paradigm in resting-state fMRI makes it much more difficult to separate the effects of motion from the underlying neural activity. The main effects of head motion are corrected using realignment of the volumes, however this does not correct secondary effects such as partial voluming, interpolation effects, magnetic field inhomogeneities, and spin-history effects [58]. These secondary effects can lead to spurious temporal correlations between brain regions even after volume realignment [59, 60]. To account for these secondary effects, participant head motion can be modelled, with the modelled responses used as regressors within the framework of a GLM [58]. However, the most effective methods for modelling and regressing motion typically result in large reductions in temporal degrees of freedom or inadvertent regression of neural signal components [61].

While the resting-state paradigm has proven beneficial for studying the functional architecture of the brain, it faces several limitations that may be hindering the development of functional connectivity as a clinical tool. If the issues of variable cognition, arousal, and head motion during scanning could be addressed, then functional connectivity may prove to be a sensitive diagnostic measure in the future.

1.4 Naturalistic Stimulation

1.4.1 Introduction

Naturalistic stimulation is a term used to describe paradigms attempting to mimic what individuals experience in a natural environment, which demands the integration of continuous streams of dynamic information [62]. Stimuli used in this context can include audiobooks, video games, and virtual reality, however the most commonly used stimulus in fMRI studies is a shortened movie or television show. This is because real-world behavior involves multiple sensory inputs that must be integrated in real-time, which can be partially recreated through

the presentation of an audiovisual stimulus such as a movie. By mimicking the natural environment, researchers can study brain function with enhanced ecological validity, allowing new questions to be asked and answered. Naturalistic stimuli also impose a behavioural constraint that, in theory, reduces the cognitive variability of individuals during scanning to create a more reproducible method of studying brain function across healthy and clinical groups [63]. Early electrophysiological studies into movie watching as an experimental paradigm demonstrated enhanced reliability of neuronal activity in the visual cortex within subjects over multiple sessions [64, 65]. These studies were followed by research validating this reliability in fMRI, where BOLD activity in early visual cortex was significantly correlated across multiple presentations of the same movie [66]. This reliability in early visual cortex was found both when the movie was played in the regular temporal direction, as well as when it was played in reverse. The BOLD signal was much less reliable in higher order areas, such as superior temporal sulcus, the frontal eye field, and the precuneus, when the movie was played in reverse, suggesting a sensitivity to the semantic and narrative aspects of the movie. Although this paradigm appears to be relatively unconstrained, and the stimuli are complex, the reliability of neural responses within subjects across multiple presentations of the same stimulus has been validated in the literature [67].

Beyond the reliability of neural responses to naturalistic stimuli across multiple scanning sessions, researchers have found that neural activity is also reliably similar across subjects. Studies investigating the effects of naturalistic stimuli have found that the fMRI time courses of activity are moderately to strongly correlated in homologous regions across a group of subjects [68, 69, 70]. The similarity of activity across subjects is typically quantified using a measure known as inter-subject correlation (ISC). To obtain the ISC, the average pairwise correlation between all subjects' fMRI time series in homologous regions is computed. One of the major benefits of this measure is that it can be used to locate activation patterns in a task without a priori knowledge of the temporal characteristics that contribute to that activation. For this reason, it has been proposed as an optimal analysis method for experiments involving complex stimuli,

where the parametric form of the stimulus in not known [71]. Although a high ISC does not necessarily imply a strong activation to a task, it has been shown that statistical spatial maps found through ISC analysis are highly similar to those found in stimulus model-based GLM analysis for simpler tasks [71]. One study showed that in a series of different tasks (auditory naming, external ordering, hand imitation, oculomotor, and verb generation), Pearson correlations between the Z-statistics of GLM and the ISC ranged from 0.69 to 0.83. A visualization of the overlap in the hand imitation task can be seen in Figure 1.4.

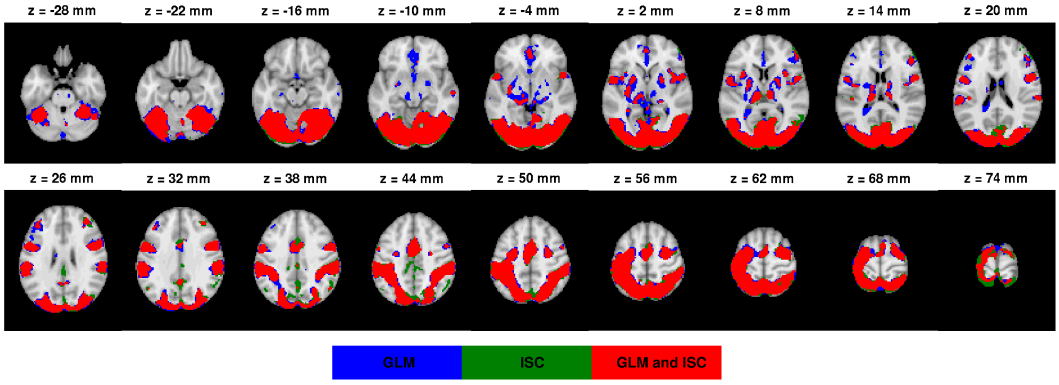

Figure 1.4: Thresholded Z-statistics of GLM and ISC (FDR corrected, q=0.001) for hand imitation task. Widespread overlap of statistically significant foci can be seen, suggesting that ISC analysis extracts similar results to traditional model-based GLM analysis. [71]

In studies investigating the movie watching condition, the highest values of ISC have generally been found in visual, auditory, and frontoparietal cortex [67, 69]. However, the topography of these patterns is dependent on the movie stimulus chosen. Previous studies have shown that widespread ISC is found for highly engaging movies, and that relative measures of engagement during the movie are related to the strength of synchronization across participants, particularly in frontal and parietal regions [69]. In movies with no narrative content or where scenes have been scrambled to remove a coherent plot, moderate ISC is typically only found in primary and association auditory and visual cortex. As would be expected, no significant ISC is found in the rest condition because there is no common stimulus to synchronize activity across subjects.

More recently, researchers have started to investigate the effects of naturalistic stimuli on functional connectivity. As stated earlier, functional connectivity is quite stable in rest and

task conditions at long time scales, and the same is true for watching a movie. One study comparing three eight-minute fMRI conditions found that the group functional connectivity topography was similar while subjects were at rest, while they watched a movie clip (Ocean's 11), and while they watched a non-narrative video stimulus (Inscapes, [72]) [73]. This study also found that the spatial patterns of intersubject variability in coupling strength were similar in all conditions. Similar to what was found by Mueller and colleagues [35] in their study of resting-state inter-subject variability, the areas with the lowest variability across subjects were in primary sensory and motor areas, while the highest was found in heteromodal association cortex.

Because of this similarity across the movie and rest conditions, a new measure was proposed in an attempt to isolate the stimulus driven components of functional connectivity when watching a movie. Inter-subject functional connectivity (ISFC) is a measure that combines ISC and FC by investigating inter-regional and inter-subject connectivity. ISFC uses the BOLD time series of a seed region in one subject's brain and looks at its correlation with the timeseries of every other region of another subject's brain [74]. The BOLD time series of each voxel is modelled as the sum of three components; a stimulus driven signal, and intrinsic signal, and a noise signal. Using this model the signal that is time-locked to the stimulus across subjects can be isolated, whereas traditional FC would capture all three signal components. Studies utilizing this measure have been able to identify static and dynamic alterations of brain connectivity in response to naturalistic stimuli, including distinctions between intrinsically and extrinsically focused networks, and alterations in the correlational structure of the DMN [74, 75]. Although the complex nature of naturalistic stimuli can make traditional forms of analysis more difficult, it creates opportunities to pose interesting questions and may provide additional benefits over traditional stimuli, as will be discussed in the next section.

1.4.2 Benefits

Proven Benefits

Although the use of naturalistic stimuli is still relatively new, several benefits of its use have already been conclusively demonstrated. These advantages are typically shown in comparison with the resting state paradigm as both are conditions with unknown temporal parameters. The first major benefit is the degree of head motion that occurs during movie watching compared to rest. Head motion is a significant issue when scanning children or individuals with certain psychological or neurological disorders [72]. Multiple studies have shown that head motion is reduced in movie watching conditions compared to rest, particularly in younger children [72, 76]. Because head motion is typically the result of restlessness in the scanner, it naturally follows that an engaging external stimulus would reduce restlessness and consequently head motion. This reduction in head motion is also seen in other task conditions as well [77]. With the previously mentioned artifactual effects that can be caused by head motion, it is important to choose a paradigm that limits its occurrence, and naturalistic stimuli appear to be a good option.

Another benefit that is seen with the use of naturalistic stimuli over rest is improved participant wakefulness. Falling asleep during scanning is of particular concern for geriatric patients, individuals taking sedative medications, and sleep-deprived participants [72]. As mentioned above, the monotony of the scanner environment in the resting-state paradigm can lead to changes in wakefulness throughout the scan. By providing participants with an audiovisual stimulus, particularly one which is engaging like a movie, self-reported measures of sleep are reduced [72, 73]. Once again, this is also true in active conditions which rarely encounter issues with sleep [78]. Because the movie increases alertness during scanning and can hold attention, it also facilitates much longer scanning times, as studies obtaining 55-minute scans or multiple 10-minute scans in one session have been conducted. [79, 80].

Finally, the naturalistic stimulation paradigm has also been shown to result in improvements

of test-retest reliability when compared to the resting-state condition. Because there is no common stimulus in the rest condition, there is no test-retest reliability of the BOLD signal, so differences are generally quantified in terms of functional connectivity. Studies comparing the two conditions have consistently shown that within-subject reliability of connectivity measures is significantly higher in the movie watching than rest condition, with one study suggesting improvements of almost 50% across a variety of functional connectivity measures [63]. This improved reliability has also been quantified through improved accuracies of test-retest matching algorithms to identify individual subjects with movie watching scans [73]. These improvements in reliability have important implications for use of functional connectivity measures in a clinical setting, particularly for individualized care. More consistent measures of functional connectivity across multiple scanning sessions increases sensitivity to changes when looking for diagnostic criteria or at the progression of a disease. If more sources of variability impact the measure than it is more difficult to separate clinically related changes from other sources of variability.

The quantifiable differences stated above are important for methodological purposes, as they each support improved validity of results in studies using naturalistic stimuli. However, there are additional hypothesized benefits, not as easily quantifiable, which will be discussed in the next section.

Hypothesized Benefits

Beyond the quantitatively demonstrated benefits of naturalistic stimuli, researchers have identified additional potential benefits. The major hypothesized advantage of a naturalistic stimulus, particularly a movie, over the resting-state condition is a synchronization of the cognitive states of individuals during the scan. While this is difficult to prove conclusively, it is reasonable to assume that neurotypical individuals will react similarly to the anticipation, excitement, and surprise which is inherent to the storyline of an engaging movie. In theory, this would result in

neural activity that is time locked to the movie stimulus and a similar functional architecture across subjects.

Naturalistic stimuli may represent a category of paradigm which reduces sources of spurious within-subject variability in functional connectivity to make similar subjects look more alike, while also eliciting reliable and meaningful idiosyncratic responses (also see [81]). These elicited differences could represent clinically relevant responses, increasing sensitivity of these paradigms to abnormal brain function.

Previous work comparing individuals with autism to neurotypical groups have indeed shown that the BOLD activity profiles of autistic participants are more variable than those of healthy participants when watching movies involving social interaction [82, 83]. The diversity of movie experiences may also allow for targeted investigations of specific traits of interest in certain groups. For example, an emotionally salient movie might be able to draw out meaningful idiosyncrasies in individuals with depression or anxiety disorders.

Naturalistic stimuli offer opportunities to probe individual and group differences in a variety of functional metrics. The lack of studies making use of naturalistic stimuli suggests that we still have much to learn about the potential translational applications of these paradigms.

1.5 Research Question

Less variable normative estimates of functional connectivity are necessary to develop adequately sensitive tests for use in a clinical setting. While intersubject variability of functional connectivity in the resting-state condition has been previously investigated, no comprehensive comparative analyses on resting-state and naturalistic stimuli have been performed. Here, I ask whether naturalistic stimulation, particularly movie watching, results in less variable estimates of functional connectivity in a healthy cohort. We believe that the behavioural constraints imposed by movie watching will result in less variable estimates of global functional connectivity

across both subjects and scanning sessions. The implication of this finding would be a potentially improved sensitivity to abnormalities in functional connectivity. The data used to resolve this question are described in the following section.

1.6 Human Connectome Project

Rapid methodological and technological advancements in imaging over the past decade, coupled with advocacy for sharing data, has spurred the creation of large, high-quality, and public brain imaging datasets. Many are based on young healthy subjects, as these individuals are typically less variable and easy to recruit, making these datasets ideal for methodological studies. The data used in this thesis have come from an NIH-funded collaboration between the University of Minnesota and Washington University, called the Human Connectome Project [84]. The goal of the project was to improve the characterization of brain function and connectivity (i.e. the connectome) in a population of 1200 young healthy adults, with efforts made to incorporate ethnic and racial diversity. This section will briefly discuss the Human Connectome Project data in terms of acquisition protocols, preprocessing pipelines, and parcellation tools.

The Human Connectome Project seeks to comprehensively describe connectivity between areas of grey matter and a variety of complementary MRI methods are employed to achieve this goal. In four hours of total imaging time, T1-weighted (T1w) and T2-weighted (T2w) structural images, BOLD functional images, and diffusion-weighted images were acquired. The diffusion-weighted acquisition will not be discussed here as the data are not used in this thesis. Both T1w and T2w images were acquired to allow for mapping of the myelin content in vivo using the ratio of the two contrasts [85]. These myelin maps are important for assessing development and aging in healthy humans and serve as useful tools for quality control because of the visibility of processing errors in the final results [86, 87]. T2w images were also acquired because of their superior accuracy over a T1w image in identifying the pial surface, as it has

similar intensity to the dura and blood vessels in a T1w image [88]. The Human Connectome Project group was interested in performing surface-based analysis on the neocortex, so optimal contrasts and high-resolution images are essential for generating high quality surface-based reconstructions. To that end, the structural images were acquired at an isotropic spatial resolution of 0.7mm, less than half of the average minimum thickness of the cortex (1.6mm) [86]. This emphasis on resolution is also true, both spatially and temporally, of the fMRI data acquired by the Human Connectome Project. Using a 7-tesla scanner, fMRI data were acquired at a spatial resolution of 1.6mm isotropic, less than the average thickness of the cortex (2.6mm) [86]. Using cutting-edge accelerated imaging protocols, volumes were acquired once per second which allows better artifact removal, statistical efficiency, and identification of faster components of the BOLD response [89, 90]. When compared to typical neuroimaging studies, where traditionally a 1-mm isotropic T1w scan and fMRI data with resolutions as low as 4mm and repetition times of 2-3 seconds are acquired, the advantages of the raw data quality are clear.

The preprocessing of acquired images in the Human Connectome Project is extensive and thoroughly described in several locations [86, 88, 91, 92]. Here, I will detail the major aspects of the pipeline and highlight notable features. Preprocessing starts by correcting intensity inhomogeneities in the T1w and T2w images, aligning both structural images together, and registering the aligned structural images to MNI space. Once the images are in MNI space, subcortical volumes are segmented into predefined structures, and Freesurfer's [93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103] surface reconstruction is applied, registering the surface to Freesurfer's fsaverage atlas [104]. Following the reconstruction, the surface is resampled onto the Human Connectome Project's symmetric fs_LR [105] atlas which contains a predefined number of surface vertices, allowing vertex to vertex comparisons across subjects. The fs_LR atlas is also symmetric, so a vertex on one hemisphere is homologous to a vertex on the opposing hemisphere, allowing easier cross-hemispheric comparisons. In the preprocessing of fMRI data, the Human Connectome Project group chose to implement non-aggressive strategies which would remove artefacts without removing potentially useful information. The

purpose of this approach was to retain as much neural signal as possible and give researchers the flexibility to implement any further preprocessing steps they believe are necessary. The spatial preprocessing of their "minimal preprocessing pipeline" involves a correction for spatial distortions caused by gradient nonlinearities, registration of volumes to a reference image to correct for head motion, registration of aligned volumes to the T1w structural image, a global intensity normalization, and finally a mapping onto the cortical surface produced by Freesurfer. The temporal preprocessing begins with the application of a weak high-pass filter with a cutoff at 0.0005 Hz and a slow rolloff of the power below that point. In addition, a technique developed in part by the Human Connectome Project team involves an ICA-based automated denoising approach, which separates the data into a series of spatiotemporal components which can be identified as having neural or non-neural origins. The components labelled as non-neural are regressed out of the data to remove their effects. This technique has been shown to be effective for removing the influence of scanner, residual motion, and physiological artefacts, and can be adjusted to be aggressive or conservative in its labelling of neural and non-neural components.

One of the major developments to have come from the Human Connectome Project dataset is the creation of the Glasser parcellation [106]. Using the multi-modal data acquired through the project, features of resting-state functional connectivity, task-based fMRI, myelin content, and cytoarchitecture were used to develop a population-based 180-area per hemisphere parcellation. The parcellation was developed using a semi-automated approach with input from neuroanatomists to identify robust and statistically separable cortical areas. While any parcellation scheme can be argued as an oversimplification of brain function, the Glasser atlas has implemented one of the most comprehensive delineations of cortical boundaries of any atlas to date (Figure 1.5). The atlas was created based on the an independent and separate 3T dataset from the subjects being used in this thesis, so we are confident that the parcellation is as reliable and robust as any other atlas currently being used.

The high-quality data, robust preprocessing approach, and innovative neuroimaging tools

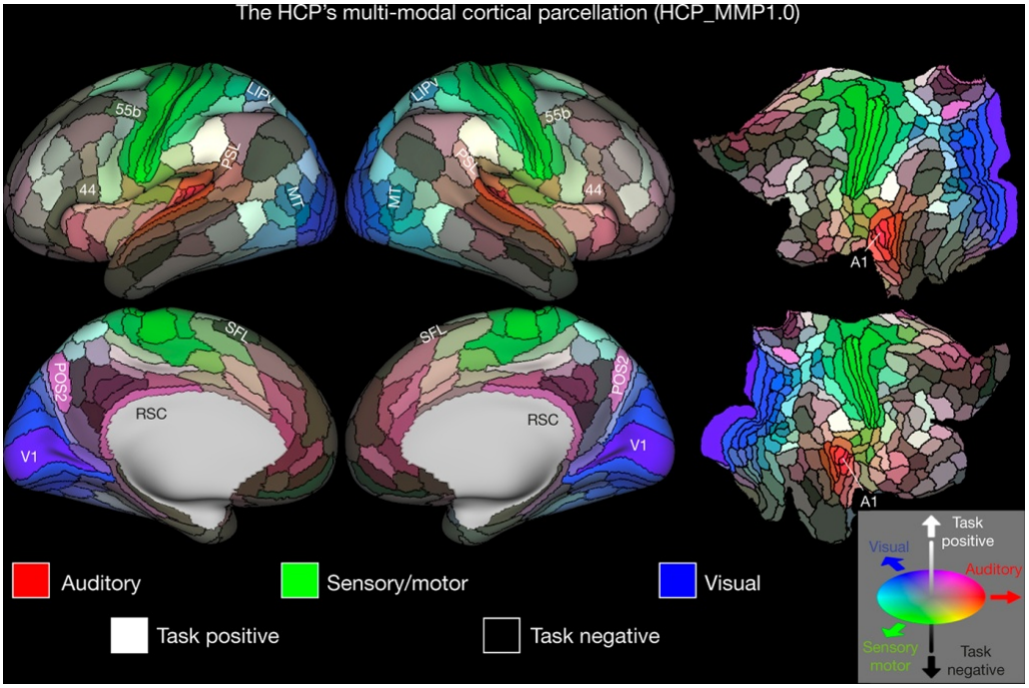

Figure 1.5: Glasser parcellation. Colouring scheme represents tendency for a region to respond to a particular task. [106]

offered by the Human Connectome Project make it an ideal dataset to test methodological questions. Following the identification of this reliable dataset, the next section will outline the objective of this thesis and the theories to be tested with the Human Connectome Project data.

1.7 Thesis Objective

The Human Connectome Project dataset allows us to quantify variability across multiple scanning sessions as well as across a large sample of subjects. We are interested in quantifying the differences in intersubject variability of functional connectivity between the resting-state and naturalistic stimulation conditions, while removing components of variability due to subject effects and noise. The method used to quantify variability in each condition is based on modelling the total observed variance into three components; a condition component representing connectivity that is similar across subjects in a particular scanning condition, an idiosyncratic

component representing connectivity that is different across subjects but consistent within a subject across multiple scanning sessions in the same condition (the subject effect), and a noise component representing connectivity that differs within a subject across multiple scanning sessions in the same condition. This concept is based on previous work which modelled the BOLD signal as the sum of a stimulus-driven signal, an intrinsic signal, and a noise signal [74].

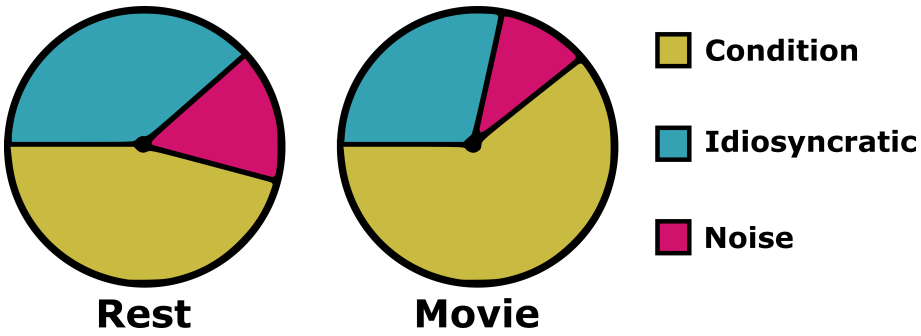

Figure 1.6: Hypothesized distribution of model components in the resting-state and movie watching conditions. Increases in the common component of functional connectivity in the movie condition should be accompanied by reductions in the idiosyncratic and noise components.

The hypothesized distribution of explained variance in each condition is visualized in Figure 1.6. We believe that the time-locked stimulus in the movie will cause functional connectivity to be more similar across subjects, thereby increasing the proportion of variance explained by the condition component. This increase in the condition component will be accompanied by reductions in the noise and idiosyncratic components.

Bibliography

[1] A. M. Morcom and P. C. Fletcher, "Does the brain have a baseline? why we should be resisting a rest," *Neuroimage*, vol. 37, no. 4, pp. 1073–1082, 2007.

[2] S. A. Huettel, A. W. Song, G. McCarthy, *et al.*, *Functional magnetic resonance imaging*, vol. 1. Sinauer Associates Sunderland, MA, 2004.

[3] P. Mansfield and A. A. Maudsley, "Medical imaging by nmr," *The British journal of radiology*, vol. 50, no. 591, pp. 188–194, 1977.

[4] F. D. Doty, G. Entzminger, J. Kulkarni, K. Pamarthy, and J. P. Staab, "Radio frequency coil technology for small-animal mri," *NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In vivo*, vol. 20, no. 3, pp. 304–325, 2007.

[5] B. Gruber, M. Froeling, T. Leiner, and D. W. Klomp, "Rf coils: A practical guide for nonphysicists," *Journal of Magnetic Resonance Imaging*, vol. 48, no. 3, pp. 590–604, 2018.

[6] F. Bloch, "Nuclear induction," *Physical review*, vol. 70, no. 7-8, p. 460, 1946.

[7] G. B. Chavhan, P. S. Babyn, B. Thomas, M. M. Shroff, and E. M. Haacke, "Principles, techniques, and applications of t2*-based mr imaging and its special applications," *Radiographics*, vol. 29, no. 5, pp. 1433–1449, 2009.

[8] S.-G. Kim and S. Ogawa, "Biophysical and physiological origins of blood oxygenation level-dependent fmri signals," *Journal of Cerebral Blood Flow & Metabolism*, vol. 32, no. 7, pp. 1188–1206, 2012.

[9] L. Pauling and C. D. Coryell, "The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin," *Proceedings of the National Academy of Sciences*, vol. 22, no. 4, pp. 210–216, 1936.

[10] N. K. Logothetis, J. Pauls, M. Augath, T. Trinath, and A. Oeltermann, "Neurophysiological investigation of the basis of the fmri signal," *Nature*, vol. 412, no. 6843, p. 150, 2001.

[11] A. Ekstrom, "How and when the fmri bold signal relates to underlying neural activity: the danger in dissociation," *Brain research reviews*, vol. 62, no. 2, pp. 233–244, 2010.

[12] M. K. Stehling, R. Turner, and P. Mansfield, "Echo-planar imaging: magnetic resonance imaging in a fraction of a second," *Science*, vol. 254, no. 5028, pp. 43–50, 1991.

[13] K. Uğurbil, "Magnetic resonance imaging at ultrahigh fields," *IEEE Transactions on Biomedical Engineering*, vol. 61, no. 5, pp. 1364–1379, 2014.

[14] B. Mišić and O. Sporns, "From regions to connections and networks: new bridges between brain and behavior," *Current opinion in neurobiology*, vol. 40, pp. 1–7, 2016.

[15] B. Biswal, F. Zerrin Yetkin, V. M. Haughton, and J. S. Hyde, "Functional connectivity in the motor cortex of resting human brain using echo-planar mri," *Magnetic resonance in medicine*, vol. 34, no. 4, pp. 537–541, 1995.

[16] T. G. Brown, "On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system," *The Journal of physiology*, vol. 48, no. 1, pp. 18–46, 1914.

[17] A. Z. Snyder and M. E. Raichle, "A brief history of the resting state: the washington university perspective," *Neuroimage*, vol. 62, no. 2, pp. 902–910, 2012.

[18] M. J. Lowe, "A historical perspective on the evolution of resting-state functional connectivity with mri," *Magnetic Resonance Materials in Physics, Biology and Medicine*, vol. 23, no. 5-6, pp. 279–288, 2010.

[19] B. Biswal, A. Hudetz, F. Z. Yetkin, V. M. Haughton, and J. S. Hyde, "Hypercapnia reversibly suppresses low-frequency fluctuations in the human motor cortex during rest using echo–planar mri," *Journal of Cerebral Blood Flow & Metabolism*, vol. 17, no. 3, pp. 301–308, 1997.

[20] B. B. Biswal, J. V. Kylen, and J. S. Hyde, "Simultaneous assessment of flow and bold signals in resting-state functional connectivity maps," *NMR in Biomedicine*, vol. 10, no. 4-5, pp. 165–170, 1997.

[21] M. E. Raichle, A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman, "A default mode of brain function," *Proceedings of the National Academy of Sciences*, vol. 98, no. 2, pp. 676–682, 2001.

[22] M. D. Greicius, B. Krasnow, A. L. Reiss, and V. Menon, "Functional connectivity in the resting brain: a network analysis of the default mode hypothesis," *Proceedings of the National Academy of Sciences*, vol. 100, no. 1, pp. 253–258, 2003.

[23] C. F. Beckmann and S. M. Smith, "Probabilistic independent component analysis for functional magnetic resonance imaging," *IEEE transactions on medical imaging*, vol. 23, no. 2, pp. 137–152, 2004.

[24] C. Rosazza, L. Minati, F. Ghielmetti, M. Mandelli, and M. Bruzzone, "Functional connectivity during resting-state functional mr imaging: Study of the correspondence between independent component analysis and region-of-interest- based methods," *American Journal of Neuroradiology*, vol. 33, no. 1, pp. 180–187, 2012.

[25] M. H. Lee, C. D. Smyser, and J. S. Shimony, "Resting-state fmri: a review of methods and clinical applications," *American Journal of Neuroradiology*, vol. 34, no. 10, pp. 1866–1872, 2013.

[26] M. D. Fox, A. Z. Snyder, J. L. Vincent, M. Corbetta, D. C. Van Essen, and M. E. Raichle, "The human brain is intrinsically organized into dynamic, anticorrelated functional networks," *Proceedings of the National Academy of Sciences*, vol. 102, no. 27, pp. 9673–9678, 2005.

[27] K. R. Van Dijk, T. Hedden, A. Venkataraman, K. C. Evans, S. W. Lazar, and R. L. Buckner, "Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization," *Journal of neurophysiology*, vol. 103, no. 1, pp. 297–321, 2009.

[28] A. T. Newton, V. L. Morgan, and J. C. Gore, "Task demand modulation of steady-state functional connectivity to primary motor cortex," *Human brain mapping*, vol. 28, no. 7, pp. 663–672, 2007.

[29] S. M. Smith, P. T. Fox, K. L. Miller, D. C. Glahn, P. M. Fox, C. E. Mackay, N. Filippini, K. E. Watkins, R. Toro, A. R. Laird, *et al.*, "Correspondence of the brain's functional architecture during activation and rest," *Proceedings of the National Academy of Sciences*, vol. 106, no. 31, pp. 13040–13045, 2009.

[30] M. W. Cole, D. S. Bassett, J. D. Power, T. S. Braver, and S. E. Petersen, "Intrinsic and task-evoked network architectures of the human brain," *Neuron*, vol. 83, no. 1, pp. 238–251, 2014.

[31] R. M. Birn, E. K. Molloy, R. Patriat, T. Parker, T. B. Meier, G. R. Kirk, V. A. Nair, M. E. Meyerand, and V. Prabhakaran, "The effect of scan length on the reliability of resting-state fmri connectivity estimates," *Neuroimage*, vol. 83, pp. 550–558, 2013.

[32] J. Gonzalez-Castillo, D. A. Handwerker, M. E. Robinson, C. W. Hoy, L. C. Buchanan, Z. S. Saad, and P. A. Bandettini, "The spatial structure of resting state connectivity stability on the scale of minutes," *Frontiers in neuroscience*, vol. 8, p. 138, 2014.

[33] C. J. Honey, R. Kötter, M. Breakspear, and O. Sporns, "Network structure of cerebral cortex shapes functional connectivity on multiple time scales," *Proceedings of the National Academy of Sciences*, vol. 104, no. 24, pp. 10240–10245, 2007.

[34] M. P. Van Den Heuvel, C. J. Stam, R. S. Kahn, and H. E. H. Pol, "Efficiency of functional brain networks and intellectual performance," *Journal of Neuroscience*, vol. 29, no. 23, pp. 7619–7624, 2009.

[35] S. Mueller, D. Wang, M. D. Fox, B. T. Yeo, J. Sepulcre, M. R. Sabuncu, R. Shafee, J. Lu, and H. Liu, "Individual variability in functional connectivity architecture of the human brain," *Neuron*, vol. 77, no. 3, pp. 586–595, 2013.

[36] J. Hill, T. Inder, J. Neil, D. Dierker, J. Harwell, and D. Van Essen, "Similar patterns of cortical expansion during human development and evolution," *Proceedings of the National Academy of Sciences*, vol. 107, no. 29, pp. 13135–13140, 2010.

[37] Z. Petanjek, M. Judaš, G. Šimić, M. R. Rašin, H. B. Uylings, P. Rakic, and I. Kostović, "Extraordinary neoteny of synaptic spines in the human prefrontal cortex," *Proceedings of the National Academy of Sciences*, vol. 108, no. 32, pp. 13281–13286, 2011.

[38] C. C. Brun, N. Leporé, X. Pennec, A. D. Lee, M. Barysheva, S. K. Madsen, C. Avedissian, Y.-Y. Chou, G. I. De Zubicaray, K. L. McMahon, *et al.*, "Mapping the regional influence of genetics on brain structure variability—a tensor-based morphometry study," *Neuroimage*, vol. 48, no. 1, pp. 37–49, 2009.

[39] G. N. Elston, T. Oga, and I. Fujita, "Spinogenesis and pruning scales across functional hierarchies," *Journal of Neuroscience*, vol. 29, no. 10, pp. 3271–3275, 2009.

[40] M. G. Kitzbichler, R. N. Henson, M. L. Smith, P. J. Nathan, and E. T. Bullmore, "Cognitive effort drives workspace configuration of human brain functional networks," *Journal of Neuroscience*, vol. 31, no. 22, pp. 8259–8270, 2011.

[41] M. N. Moussa, C. D. Vechlekar, J. H. Burdette, M. R. Steen, C. E. Hugenschmidt, and P. J. Laurienti, "Changes in cognitive state alter human functional brain networks," *Frontiers in human neuroscience*, vol. 5, p. 83, 2011.

[42] K. Friston, C. Buechel, G. Fink, J. Morris, E. Rolls, and R. J. Dolan, "Psychophysiological and modulatory interactions in neuroimaging," *Neuroimage*, vol. 6, no. 3, pp. 218–229, 1997.

[43] D. V. Smith, M. Gseir, M. E. Speer, and M. R. Delgado, "Toward a cumulative science of functional integration: a meta-analysis of psychophysiological interactions," *Human brain mapping*, vol. 37, no. 8, pp. 2904–2917, 2016.

[44] L. Geerligs, M. Rubinov, R. N. Henson, *et al.*, "State and trait components of functional connectivity: individual differences vary with mental state," *Journal of Neuroscience*, vol. 35, no. 41, pp. 13949–13961, 2015.

[45] R. M. Hutchison, T. Womelsdorf, E. A. Allen, P. A. Bandettini, V. D. Calhoun, M. Corbetta, S. Della Penna, J. H. Duyn, G. H. Glover, J. Gonzalez-Castillo, *et al.*, "Dynamic functional connectivity: promise, issues, and interpretations," *Neuroimage*, vol. 80, pp. 360–378, 2013.

[46] P. Delamillieure, G. Doucet, B. Mazoyer, M.-R. Turbelin, N. Delcroix, E. Mellet, L. Zago, F. Crivello, L. Petit, N. Tzourio-Mazoyer, *et al.*, "The resting state questionnaire: an introspective questionnaire for evaluation of inner experience during the conscious resting state," *Brain research bulletin*, vol. 81, no. 6, pp. 565–573, 2010.

[47] K. J. Gorgolewski, D. Lurie, S. Urchs, J. A. Kipping, R. C. Craddock, M. P. Milham, D. S. Margulies, and J. Smallwood, "A correspondence between individual differences in the brain's intrinsic functional architecture and the content and form of self-generated thoughts," *PloS one*, vol. 9, no. 5, p. e97176, 2014.

[48] D. Stoffers, B. A. Diaz, G. Chen, A. den Braber, D. van't Ent, D. I. Boomsma, H. D. Mansvelder, E. de Geus, E. J. Van Someren, and K. Linkenkaer-Hansen, "Resting-state fmri functional connectivity is associated with sleepiness, imagery, and discontinuity of mind," *PloS one*, vol. 10, no. 11, p. e0142014, 2015.

[49] M. Greicius, "Resting-state functional connectivity in neuropsychiatric disorders," *Current opinion in neurology*, vol. 21, no. 4, pp. 424–430, 2008.

[50] M. D. Fox and M. Greicius, "Clinical applications of resting state functional connectivity," *Frontiers in systems neuroscience*, vol. 4, p. 19, 2010.

[51] M. D. Greicius, G. Srivastava, A. L. Reiss, and V. Menon, "Default-mode network activity distinguishes alzheimer's disease from healthy aging: evidence from functional mri," *Proceedings of the National Academy of Sciences*, vol. 101, no. 13, pp. 4637–4642, 2004.

[52] M. D. Greicius, B. H. Flores, V. Menon, G. H. Glover, H. B. Solvason, H. Kenna, A. L. Reiss, and A. F. Schatzberg, "Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus," *Biological psychiatry*, vol. 62, no. 5, pp. 429–437, 2007.

[53] A. Anand, Y. Li, Y. Wang, J. Wu, S. Gao, L. Bukhari, V. P. Mathews, A. Kalnin, and M. J. Lowe, "Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study," *Biological psychiatry*, vol. 57, no. 10, pp. 1079–1088, 2005.

[54] B. A. Diaz, S. Van Der Sluis, S. Moens, J. S. Benjamins, F. Migliorati, D. Stoffers, A. Den Braber, S.-S. Poil, R. Hardstone, D. Van't Ent, *et al.*, "The amsterdam resting-state questionnaire reveals multiple phenotypes of resting-state cognition," *Frontiers in human neuroscience*, vol. 7, p. 446, 2013.

[55] S. Richter, K. Marsalek, C. Glatz, and A. Gundel, "Task-dependent differences in subjective fatigue scores," *Journal of sleep research*, vol. 14, no. 4, pp. 393–400, 2005.

[56] E. Tagliazucchi and H. Laufs, "Decoding wakefulness levels from typical fmri resting-state data reveals reliable drifts between wakefulness and sleep," *Neuron*, vol. 82, no. 3, pp. 695–708, 2014.

[57] A. Chaudhuri and P. O. Behan, "Fatigue in neurological disorders," *The lancet*, vol. 363, no. 9413, pp. 978–988, 2004.

[58] K. J. Friston, S. Williams, R. Howard, R. S. Frackowiak, and R. Turner, "Movement-related effects in fmri time-series," *Magnetic resonance in medicine*, vol. 35, no. 3, pp. 346–355, 1996.

[59] J. D. Power, K. A. Barnes, A. Z. Snyder, B. L. Schlaggar, and S. E. Petersen, "Spurious but systematic correlations in functional connectivity mri networks arise from subject motion," *Neuroimage*, vol. 59, no. 3, pp. 2142–2154, 2012.

[60] K. R. Van Dijk, M. R. Sabuncu, and R. L. Buckner, "The influence of head motion on intrinsic functional connectivity mri," *Neuroimage*, vol. 59, no. 1, pp. 431–438, 2012.

[61] L. Parkes, B. Fulcher, M. Yücel, and A. Fornito, "An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional mri," *Neuroimage*, vol. 171, pp. 415–436, 2018.

[62] K. L. Bottenhorn, J. S. Flannery, E. R. Boeving, M. C. Riedel, S. B. Eickhoff, M. T. Sutherland, and A. R. Laird, "Cooperating yet distinct brain networks engaged during naturalistic paradigms: A meta-analysis of functional mri results," *Network Neuroscience*, vol. 3, no. 1, pp. 27–48, 2018.

[63] J. Wang, Y. Ren, X. Hu, V. T. Nguyen, L. Guo, J. Han, and C. C. Guo, "Test–retest reliability of functional connectivity networks during naturalistic fmri paradigms," *Human brain mapping*, vol. 38, no. 4, pp. 2226–2241, 2017.

[64] H. Yao, L. Shi, F. Han, H. Gao, and Y. Dan, "Rapid learning in cortical coding of visual scenes," *Nature neuroscience*, vol. 10, no. 6, p. 772, 2007.

[65] A. Belitski, A. Gretton, C. Magri, Y. Murayama, M. A. Montemurro, N. K. Logothetis, and S. Panzeri, "Low-frequency local field potentials and spikes in primary visual cortex convey independent visual information," *Journal of Neuroscience*, vol. 28, no. 22, pp. 5696–5709, 2008.

[66] U. Hasson, E. Yang, I. Vallines, D. J. Heeger, and N. Rubin, "A hierarchy of temporal receptive windows in human cortex," *Journal of Neuroscience*, vol. 28, no. 10, pp. 2539–2550, 2008.

[67] U. Hasson, R. Malach, and D. J. Heeger, "Reliability of cortical activity during natural stimulation," *Trends in cognitive sciences*, vol. 14, no. 1, pp. 40–48, 2010.

[68] U. Hasson, Y. Nir, I. Levy, G. Fuhrmann, and R. Malach, "Intersubject synchronization of cortical activity during natural vision," *science*, vol. 303, no. 5664, pp. 1634–1640, 2004.

[69] L. Naci, R. Cusack, M. Anello, and A. M. Owen, "A common neural code for similar conscious experiences in different individuals," *Proceedings of the National Academy of Sciences*, vol. 111, no. 39, pp. 14277–14282, 2014.

[70] J.-P. Kauppi, I. P. Jääskeläinen, M. Sams, and J. Tohka, "Inter-subject correlation of brain hemodynamic responses during watching a movie: localization in space and frequency," *Frontiers in neuroinformatics*, vol. 4, p. 5, 2010.

[71] J. Pajula, J.-P. Kauppi, and J. Tohka, "Inter-subject correlation in fmri: method validation against stimulus-model based analysis," *PloS one*, vol. 7, no. 8, p. e41196, 2012.

[72] T. Vanderwal, C. Kelly, J. Eilbott, L. C. Mayes, and F. X. Castellanos, "Inscapes: A movie paradigm to improve compliance in functional magnetic resonance imaging," *Neuroimage*, vol. 122, pp. 222–232, 2015.

[73] T. Vanderwal, J. Eilbott, E. S. Finn, R. C. Craddock, A. Turnbull, and F. X. Castellanos, "Individual differences in functional connectivity during naturalistic viewing conditions," *Neuroimage*, vol. 157, pp. 521–530, 2017.

[74] E. Simony, C. J. Honey, J. Chen, O. Lositsky, Y. Yeshurun, A. Wiesel, and U. Hasson, "Dynamic reconfiguration of the default mode network during narrative comprehension," *Nature communications*, vol. 7, p. 12141, 2016.

[75] Y. Ren, V. T. Nguyen, L. Guo, and C. C. Guo, "Inter-subject functional correlation reveal a hierarchical organization of extrinsic and intrinsic systems in the brain," *Scientific reports*, vol. 7, no. 1, p. 10876, 2017.

[76] D. J. Greene, J. M. Koller, J. M. Hampton, V. Wesevich, A. N. Van, A. L. Nguyen, C. R. Hoyt, L. McIntyre, E. A. Earl, R. L. Klein, *et al.*, "Behavioral interventions for reducing head motion during mri scans in children," *Neuroimage*, vol. 171, pp. 234–245, 2018.

[77] W. Huijbers, K. R. Van Dijk, M. M. Boenniger, R. Stirnberg, and M. M. Breteler, "Less head motion during mri under task than resting-state conditions," *NeuroImage*, vol. 147, pp. 111–120, 2017.

[78] L. M. Shah, J. A. Cramer, M. A. Ferguson, R. M. Birn, and J. S. Anderson, "Reliability and reproducibility of individual differences in functional connectivity acquired during task and resting state," *Brain and behavior*, vol. 6, no. 5, p. e00456, 2016.

[79] J. S. Anderson, M. A. Ferguson, M. Lopez-Larson, and D. Yurgelun-Todd, "Reproducibility of single-subject functional connectivity measurements," *American journal of neuroradiology*, vol. 32, no. 3, pp. 548–555, 2011.

[80] M. R. Sabuncu, B. D. Singer, B. Conroy, R. E. Bryan, P. J. Ramadge, and J. V. Haxby, "Function-based intersubject alignment of human cortical anatomy," *Cerebral cortex*, vol. 20, no. 1, pp. 130–140, 2009.

[81] E. S. Finn, D. Scheinost, D. M. Finn, X. Shen, X. Papademetris, and R. T. Constable, "Can brain state be manipulated to emphasize individual differences in functional connectivity?," *Neuroimage*, vol. 160, pp. 140–151, 2017.

[82] L. Byrge, J. Dubois, J. M. Tyszka, R. Adolphs, and D. P. Kennedy, "Idiosyncratic brain activation patterns are associated with poor social comprehension in autism," *Journal of Neuroscience*, vol. 35, no. 14, pp. 5837–5850, 2015.

[83] J. Salmi, U. Roine, E. Glerean, J. Lahnakoski, T. Nieminen-von Wendt, P. Tani, S. Leppämäki, L. Nummenmaa, I. P. Jääskeläinen, S. Carlson, *et al.*, "The brains of high functioning autistic individuals do not synchronize with those of others," *NeuroImage: Clinical*, vol. 3, pp. 489–497, 2013.

[84] D. C. Van Essen, S. M. Smith, D. M. Barch, T. E. Behrens, E. Yacoub, K. Ugurbil, W.-M. H. Consortium, *et al.*, "The wu-minn human connectome project: an overview," *Neuroimage*, vol. 80, pp. 62–79, 2013.

[85] M. F. Glasser and D. C. Van Essen, "Mapping human cortical areas in vivo based on myelin content as revealed by t1-and t2-weighted mri," *Journal of Neuroscience*, vol. 31, no. 32, pp. 11597–11616, 2011.

[86] M. F. Glasser, S. M. Smith, D. S. Marcus, J. L. Andersson, E. J. Auerbach, T. E. Behrens, T. S. Coalson, M. P. Harms, M. Jenkinson, S. Moeller, *et al.*, "The human connectome project's neuroimaging approach," *Nature neuroscience*, vol. 19, no. 9, p. 1175, 2016.

[87] A. Hagiwara, M. Hori, K. Kamagata, M. Warntjes, D. Matsuyoshi, M. Nakazawa, R. Ueda, C. Andica, S. Koshino, T. Maekawa, *et al.*, "Myelin measurement: Comparison between simultaneous tissue relaxometry, magnetization transfer saturation index, and t 1 w/t 2 w ratio methods," *Scientific reports*, vol. 8, no. 1, p. 10554, 2018.

[88] M. F. Glasser, S. N. Sotiropoulos, J. A. Wilson, T. S. Coalson, B. Fischl, J. L. Andersson, J. Xu, S. Jbabdi, M. Webster, J. R. Polimeni, *et al.*, "The minimal preprocessing pipelines for the human connectome project," *Neuroimage*, vol. 80, pp. 105–124, 2013.

[89] L. Griffanti, G. Salimi-Khorshidi, C. F. Beckmann, E. J. Auerbach, G. Douaud, C. E. Sexton, E. Zsoldos, K. P. Ebmeier, N. Filippini, C. E. Mackay, *et al.*, "Ica-based artefact removal and accelerated fmri acquisition for improved resting state network imaging," *Neuroimage*, vol. 95, pp. 232–247, 2014.

[90] J. E. Chen and G. H. Glover, "Bold fractional contribution to resting-state functional connectivity above 0.1 hz," *Neuroimage*, vol. 107, pp. 207–218, 2015.

[91] S. M. Smith, C. F. Beckmann, J. Andersson, E. J. Auerbach, J. Bijsterbosch, G. Douaud, E. Duff, D. A. Feinberg, L. Griffanti, M. P. Harms, *et al.*, "Resting-state fmri in the human connectome project," *Neuroimage*, vol. 80, pp. 144–168, 2013.

[92] E. C. Robinson, S. Jbabdi, M. F. Glasser, J. Andersson, G. C. Burgess, M. P. Harms, S. M. Smith, D. C. Van Essen, and M. Jenkinson, "Msm: a new flexible framework for multimodal surface matching," *Neuroimage*, vol. 100, pp. 414–426, 2014.

[93] A. Dale, B. Fischl, and M. I. Sereno, "Cortical surface-based analysis: I. segmentation and surface reconstruction," *NeuroImage*, vol. 9, no. 2, pp. 179 – 194, 1999.

[94] A. M. Dale and M. I. Sereno, "Improved localizadon of cortical activity by combining eeg and meg with mri cortical surface reconstruction: a linear approach," *Journal of cognitive neuroscience*, vol. 5, no. 2, pp. 162–176, 1993.

[95] B. Fischl and A. M. Dale, "Measuring the thickness of the human cerebral cortex from magnetic resonance images," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 20, pp. 11050–11055, 2000.

[96] B. Fischl, A. Liu, and A. M. Dale, "Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex," *IEEE Medical Imaging*, vol. 20, pp. 70–80, Jan 2001.

[97] B. Fischl, D. H. Salat, E. Busa, M. Albert, M. Dieterich, C. Haselgrove, A. van der Kouwe, R. Killiany, D. Kennedy, S. Klaveness, A. Montillo, N. Makris, B. Rosen, and A. M. Dale, "Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain," *Neuron*, vol. 33, pp. 341–355, 2002.

[98] B. Fischl, D. H. Salat, A. J. van der Kouwe, N. Makris, F. Ségonne, B. T. Quinn, and A. M. Dale, "Sequence-independent segmentation of magnetic resonance images," *NeuroImage*, vol. 23, no. Supplement 1, pp. S69 – S84, 2004. Mathematics in Brain Imaging.

[99] B. Fischl, M. I. Sereno, and A. M. Dale, "Cortical surface-based analysis: Ii: inflation, flattening, and a surface-based coordinate system," *Neuroimage*, vol. 9, no. 2, pp. 195–207, 1999.

[100] B. Fischl, A. van der Kouwe, C. Destrieux, E. Halgren, F. Ségonne, D. H. Salat, E. Busa, L. J. Seidman, J. Goldstein, D. Kennedy, V. Caviness, N. Makris, B. Rosen, and A. M. Dale, "Automatically Parcellating the Human Cerebral Cortex," *Cerebral Cortex*, vol. 14, no. 1, pp. 11–22, 2004.

[101] X. Han, J. Jovicich, D. Salat, A. van der Kouwe, B. Quinn, S. Czanner, E. Busa, J. Pacheco, M. Albert, R. Killiany, *et al.*, "Reliability of mri-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer," *Neuroimage*, vol. 32, no. 1, pp. 180–194, 2006.

[102] J. Jovicich, S. Czanner, D. Greve, E. Haley, A. van der Kouwe, R. Gollub, D. Kennedy, F. Schmitt, G. Brown, J. MacFall, B. Fischl, and A. Dale, "Reliability in multi-site structural mri studies: Effects of gradient non-linearity correction on phantom and human data," *NeuroImage*, vol. 30, no. 2, pp. 436 – 443, 2006.

[103] F. Segonne, A. M. Dale, E. Busa, M. Glessner, D. Salat, H. K. Hahn, and B. Fischl, "A hybrid approach to the skull stripping problem in mri," *NeuroImage*, vol. 22, no. 3, pp. 1060 – 1075, 2004.

[104] B. Fischl, M. I. Sereno, R. B. Tootell, and A. M. Dale, "High-resolution intersubject averaging and a coordinate system for the cortical surface," *Human Brain Mapping*, vol. 8, no. 4, pp. 272–284, 1999.

[105] D. C. Van Essen, M. F. Glasser, D. L. Dierker, J. Harwell, and T. Coalson, "Parcellations and hemispheric asymmetries of human cerebral cortex analyzed on surface-based atlases," *Cerebral cortex*, vol. 22, no. 10, pp. 2241–2262, 2011.

[106] M. F. Glasser, T. S. Coalson, E. C. Robinson, C. D. Hacker, J. Harwell, E. Yacoub, K. Ugurbil, J. Andersson, C. F. Beckmann, M. Jenkinson, *et al.*, "A multi-modal parcellation of human cerebral cortex," *Nature*, vol. 536, no. 7615, p. 171, 2016.

Chapter 2

Individual Variability of Functional Connectivity in Resting-State and Movie Watching fMRI Paradigms

2.1 Introduction

For over two decades, functional magnetic resonance imaging (fMRI) research has attempted to characterize the interregional relationships of the human brain. The existence of temporal correlations between the low-frequency (0.001 – 0.1 Hz) spontaneous hemodynamic fluctuations of functionally congruent brain areas was first discovered by Biswal and colleagues in 1995 [1] and is now well established in the functional-imaging literature. These correlations have been primarily studied in the resting-state condition, when no direct stimulus is applied to the subject. A variety of analytical methods for studying functional connectivity (FC) have been implemented with resting-state fMRI data, establishing that the network structures at the group level are quite robust [2, 3]. When studied at long time scales, the group-level whole-brain FC architecture is consistent across multiple task paradigms as well [4]. However, recent resting-state fMRI studies have suggested that connection strengths can vary across the duration of the scan [5], between sessions [6], and between different cognitive states [7, 8]. For decades the study of psychophysiological interactions in task-based fMRI studies have indicated that altered cognitive states have focal effects on certain connections based on the task paradigm used

[9, 10]. Because cognitive states are unconstrained in the resting state, they may vary across individuals and cause increased variability in estimates of FC. This has recently been explored in relation to global FC, where similarity of FC matrices across participants have been shown to be higher in task-based paradigms than in resting-state fMRI [8, 11]. The increased individual variability in the resting-state condition may reduce the sensitivity of coupling measures to group differences, an important consideration when studying clinical populations.

Resting-state FC has been extensively investigated as a clinical measure and is widely believed to be a potential biomarker for diseases such as Alzheimer's [12], depression [13], and schizophrenia [14]. The promise of resting-state FC as a diagnostic tool relies on it identifying abnormalities in the connectivity structure that also have a relationship with clinical features. Ideally, when studying the correlational structure of a group of healthy controls, one would like to suppress idiosyncratic differences within the group to obtain an estimate of healthy FC that is less variable. Reduced variability in the connectivity estimates would allow for greater sensitivity to abnormal connectivity, as the disease-specific differences would not be lost in general idiosyncratic variability.

Although the resting-state paradigm has produced valuable insights into the FC architecture, it has been criticized due to its lack of control over the cognitive states of individuals during scanning [15, 16]. This makes the interpretation of any conclusions, beyond those related to physiology, mostly speculative. However, a new paradigm has emerged that makes use of naturalistic stimuli – movies or audiobooks - in an attempt to synchronize the cognitive states of individuals throughout the duration of the scan [17, 18]. In these paradigms, a group of participants watching the same movie or listening to the same story appears to engage brain regions responsible for higher order cognitive functions as well as primary sensory areas, resulting in stereotyped time courses of activity that are time-locked to the stimulus [19]. Studies investigating the effects of naturalistic stimuli typically find that these time courses of activity are strongly correlated in homologous regions across a group of subjects. The highest values of this inter-subject correlation (ISC) in studies involving movie watching have generally been

found in visual, auditory, and frontoparietal cortex [18, 19]. This would be expected as the audiovisual stimulus aligns activity in the visual and auditory regions, and the higher-order cognitive demands of the movie, such as anticipation and suspense, align activity in frontoparietal regions [19]. Naturalistic stimuli provide researchers with an opportunity to study whole brain activity in a more ecologically valid way, providing a middle ground between fully unconstrained cognition at rest and narrowly focused cognition during traditional task-based paradigms.

With the newly released 7T resting-state and movie stimulation data from the Human Connectome Project [20], we have a unique opportunity to study the connectivity architecture in both conditions, as well as compare the inter-individual variability that each condition evokes. The Human Connectome Project is an NIH funded collaboration between the University of Minnesota and Washington University, which aims to characterize brain connectivity and function in a large group of healthy adults. The public data set provides four 15-minute scanning sessions of each participant for each condition with exceptional spatial and temporal resolution in image acquisitions and a validated preprocessing approach.

The BOLD signal underlying FC has previously been modelled as a summation of a stimulus-driven signal, an idiosyncratic neural signal, and a non-neural signal [21]. In this model, the stimulus-driven signal is common across all subjects, while the idiosyncratic and non-neural components vary across subjects. This model has been used in naturalistic paradigm studies to extract the stimulus-driven components of connectivity that are directly influenced by the movie [22]. We aim to model FC in a similar manner here, by exploiting multiple sessions in each condition. Because we have a stimulus-free resting-state condition, we model the stimulus-driven component simply as a condition-based contribution to FC variance, representing connectivity which is consistent across subjects in a particular condition. Additionally, we include an idiosyncratic subject-specific contribution, representing connectivity that is consistent within a subject across sessions but differs between subjects in a condition, and a contribution that is inconsistent across both sessions and subjects, which we label as noise.

In the current study, we aim to quantify the contributions to variance from the components of our model in both resting-state and movie-watching conditions. We hypothesize that the idiosyncratic contribution to variance will be reduced in auditory, visual, and frontoparietal cortices in the movie condition when compared to rest, because of the time-locked nature of movie. In the second part of the study, we compute the ISC values in the movie condition to characterize BOLD signal synchronization across subjects. Because ISC suggests synchronous cognitive states across people, we should observe high ISC values in areas with less variable connectivity values – in other words, in areas in which the idiosyncratic subject effects are smaller in the movie, compared to rest.

To our knowledge, only one previous study has attempted to quantify and directly compare the inter-individual variability of FC in movie-watching and resting-state fMRI paradigms in a group of healthy subjects [23]. The study involved the acquisition of one run in a resting state, one run presenting a non-verbal and non-social abstract video clip, and one run presenting a clip from the film Ocean's 11, with each lasting 7 minutes and 20 seconds. The researchers quantified intersubject variability by regressing split-half correlations of FC measures within subjects from subject-wise correlations of FC within a condition and using the residuals as a measure of true inter-individual variability. The researchers found that the spatial distribution of intersubject variability in both the rest and movie conditions were similar, and was consistent with what had previously been found in resting-state alone [24]. They also found that the magnitude of intersubject variability was similar across conditions. However, the study has crucial limitations that may impede its ability to identify differences between conditions. Primarily, the study only acquired one scan per condition for each subject, making it difficult to accurately assess intrasubject variability. The authors chose to examine split-half correlations to estimate intrasubject variability, but this results in only 3 minutes and 40 seconds of data being used to estimate FC for each half. It has been shown that 5-7 minutes of fMRI data is required to achieve reliable individual connectivity estimates [25]. Our study includes four 15-minute scans per condition for each subject, allowing for a reliable assessment of intrasub-

ject variability across multiple scanning sessions. The use of multiple scans also provides a more accurate depiction of the components of FC that are consistently similar across subjects over repeated measures. Additionally, our sample size of 79 subjects is much larger than the previous study which only boasted a cohort of 31 subjects. Finally, we extend our discussion beyond the previous work by investigating the relationship between intersubject FC variability differences across conditions and the ISC observed in the movie condition.

2.2 Methods

2.2.1 Human Connectome Project Data

Minimally preprocessed data from 79 subjects were obtained from the Washington University-University of Minnesota Consortium of the Human Connectome Project [26] (38 M/41 F, Age 22-36), with each subject providing four resting-state runs and four movie-watching runs, each 15 minutes long. All fMRI data were collected in four scanning sessions over two days using a Siemens Magnetom 7T MR scanner (SC72 gradient coil 70–100 mT/m, multiband factor of 5, echo time = 22 ms, repetition time = 1 s, 1.6 mm isotropic voxel size) [27, 28]. Resting-state scans were acquired at the beginning of each scanning session. In these, participants were instructed to fixate on a projected bright cross-hair on a dark background. Following the resting-state run in the first and fourth scanning sessions, participants were shown one run of four concatenated independently produced movie clips, ranging from 64 to 244 seconds separated by 20 seconds of rest. This was followed by one run of three concatenated Hollywood movie clips ranging from 227 to 259 seconds separated by 20 seconds of rest. The movie clips were different across the four runs and may drive cognition differently over time, however each of the four movie stimuli ended with an identical short clip (83 seconds) for validation across scans. The HCP minimal preprocessing pipeline has been described elsewhere and should be referred to for extended details about their preprocessing approach [29].

2.2.2 Global Functional Connectivity

An anatomical parcellation based on multimodal data [30], in the same stereotaxic space as the normalized individual data (fs_LR, [31]) was applied to identify 180 regions of interest (ROI) per hemisphere in the cerebral cortex. Subcortical structures and cerebellum were excluded from this analysis.

We began by computing FC measures in each run of each condition for each participant. To obtain this, the time series of all vertices contained in a given parcel were averaged to obtain a single mean time series for each ROI. A correlation matrix was obtained for each subject in each run in both conditions - eight matrices per subject - by computing the temporal correlation (Pearson r) between each pair of ROI time series, providing 64,620 unique correlation values per matrix. To assess differences in connectivity structure between conditions, we computed a group-averaged connectivity matrix for each condition. To make the distribution of FC values more normal before group averaging, the correlation values were converted to z scores using the Fisher r-to-z transformation and then averaged across subjects and runs within each condition. The final group correlation matrices were obtained by converting the Fisher z scores back into Pearson r values, resulting in one group matrix per condition.

With estimates of FC for each subject, we proceeded to examine the sample variance of FC for each node (i.e. each unique ROI pair) in the matrix. This resulted in a second matrix of correlation variance values for each condition providing a overall measure of how variable FC estimates were across subjects.

2.2.3 Variance Contributions

Once FC values were obtained for each run of each condition in all subjects, we proceeded to estimate the contributions to variance. The method for computing the contributions to variance is illustrated in Figure 2.1. We model the explained variance of FC as the combination of a con-

dition component, an idiosyncratic subject-specific component, and variance that is explained by neither case, which we label as noise. Using the FC matrices computed in the previous section, we can use the columns of the matrix as correlational maps for each ROI, indexing the correlation values between it and every other ROI in the parcellation (1 x 360 vector). These maps serve as a fingerprint of how one region connects with every other region in the brain in a particular session for a particular subject. These will be referred to as "connectivity fingerprints". To quantify the similarity of an ROI's connectivity across subjects, we computed the pairwise correlation of an ROI's connectivity fingerprint between all unique pairs of subjects and averaged the pairwise correlations to obtain one measure of similarity (r_{cond}) per condition. In a similar manner, the reliability of connectivity fingerprints across sessions was quantified by computing the pairwise correlation of an ROI's connectivity fingerprint across all four sessions within a subject in a condition and averaging the pairwise correlations of all subjects within a condition to obtain a measure of reliability (r_{sess}) per condition.

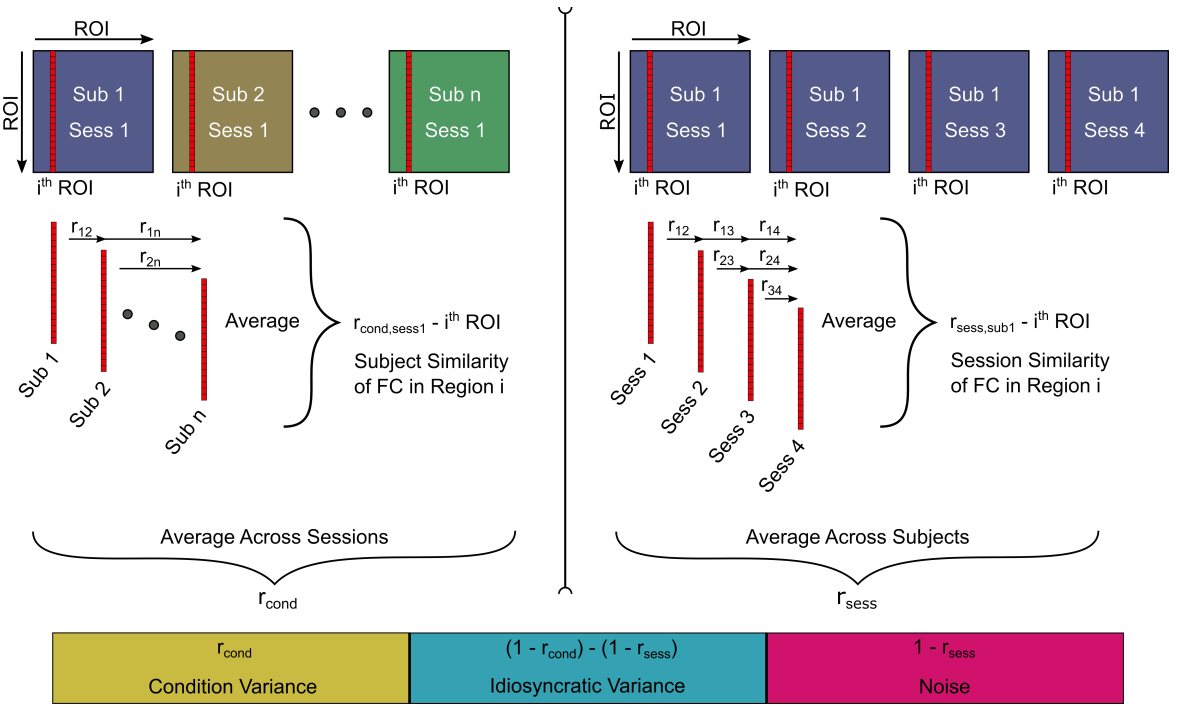

Figure 2.1: Schematic depicting the analysis method use to calculate the three contributions to variance in our model. Beginning with functional connectivity matrices for each subject's four sessions, average subject and session similarity measures are obtained and used to compute final estimates.

In our model of variance contributions, we denote the complement of r_{sess} as a measure of noise. This is because the proportion of connectivity which is unreliable across sessions of a condition cannot be attributed to intersubject or inter-condition differences. The complement of r_{cond} is believed to represent a combination of this noise as well as idiosyncratic subject-specific variability. To isolate the proportion of idiosyncratic variability within a condition, we take the difference between the complements of r_{sess} and r_{cond}. Finally, the proportion of condition variability, representing connectivity that is similar across subjects within a condition, is simply r_{cond}.

2.2.4 Inter-Subject Correlation

As in previous studies, ISC values were obtained by extracting the time series for ROIs across all subjects, computing the Pearson correlation between the time series in homologous regions across all unique pairs of subjects, and averaging all pairwise correlations to obtain one value per ROI [17, 32]. This procedure was performed both at the parcel level as well as the voxel level to ensure the parcellation accurately captured the level of synchronization of BOLD activity across subjects. A subject-wise bootstrapping approach was performed to create a null distribution allowing statistical thresholding of the ISC results [33].

2.2.5 Statistical Testing

Glasser and colleagues have organized the 360 parcels of their atlas into 22 larger regions based on geographic proximity and functional similarity (Figure 2.2A) [30]. Based on previous movie stimulation studies showing strong ISC in frontal, auditory, and visual regions, we identified 10 of these regions as most likely to demonstrate differences in FC variance between the rest and movie conditions. These regions are detailed in Table 2.1 and visualized in Figure 2.2B.

Table 2.1: List of important ROIs in larger Glasser regions seen in figure 2.2A. The ROIs were grouped into areas representing visual auditory, and frontal cortex.

Grouping	**Regions**
Visual Areas	(1) – Primary Visual Cortex (2) – Early Visual Cortex (3) – Dorsal Stream Visual Cortex (4) – Ventral Stream Visual Cortex (5) – MT+ Complex
Auditory Areas	(10) – Early Auditory Cortex (11) – Auditory Association Cortex
Frontal Areas	(19) – Anterior Cingulate and Medial Prefrontal Cortex (21) – Inferior Frontal Cortex (22) – Dorsolateral Prefrontal Cortex

To test for significant differences between conditions and variance contributions, two-way repeated measures ANOVAs were conducted for each grouping. Because the idiosyncratic variance contribution is a derived measure, there is only one degree of freedom for the variance contribution factor. For this reason, the ANOVA only includes common and idiosyncratic contributions as levels of the variance contribution factor. To test for differences in the noise contribution, t-tests were conducted between conditions for each grouping.

2.3 Results

2.3.1 Global Functional Connectivity

FC matrices have been organized by functional similarity and geographic proximity for visualization purposes (Figure 2.3). At the group level, averaging across all four sessions for each condition, the FC matrices for the resting-state and movie conditions were strongly correlated with one another (r = 0.865). This aligns with previous work noting similar correlational struc-

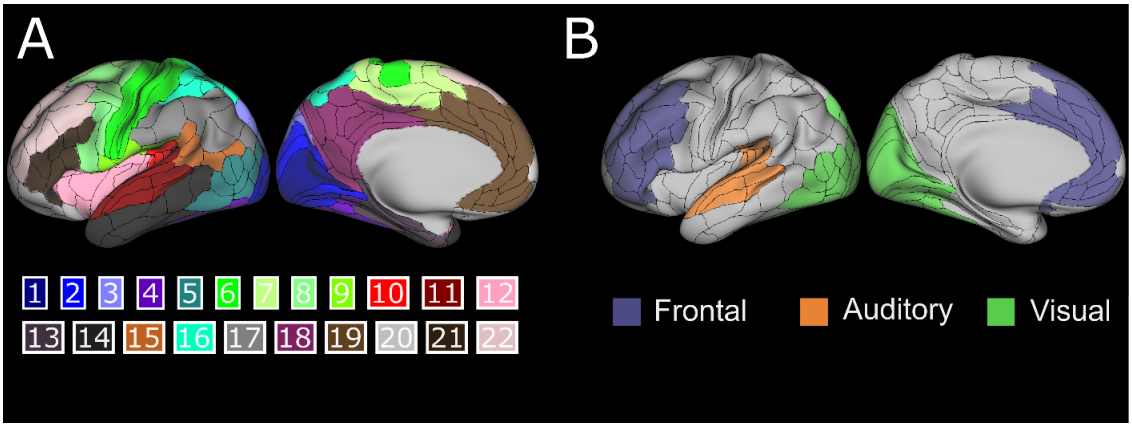

Figure 2.2: (A) 22 Groupings of parcels based on geographic proximity and functional similarity. (Adapted from Glasser et al. [30]), (B) Identification of frontal, auditory, and visual regions likely to demonstrate differences between the resting-state and movie conditions

tures between rest and movie or task conditions [4, 8]. Both matrices show strong intra-network connectivity and low inter-network connectivity. Connectivity strengths tended to be slightly higher in the rest condition (mean = 0.231, SD = 0.161) than in the movie condition (mean = 0.196, SD = 0.162). The mean intersubject variance across all connections was slightly lower in the movie condition (mean = 0.022, SD = 0.007) than the rest condition (mean = 0.027, SD = 0.007) (figure 2.3B).

2.3.2 Contributions to Variance Differ Across Conditions

In our model, we estimate contributions from three different sources of variability, a condition component, an idiosyncratic subject-specific component, and a noise component. For easier interpretations of the results, we present difference maps indicating the areas where component estimates were higher in the resting-state condition and areas where estimates were higher in the movie condition (Figure 2.4). Regions with larger proportions of condition variability in rest than movie were much more widespread, indicating that connectivity was more similar across participants in the movie-watching condition than the resting-state condition for most regions. These differences were largest in superior and inferior temporal cortex, areas known to be involved in the processing of sensory input. These difference maps can be seen in the top

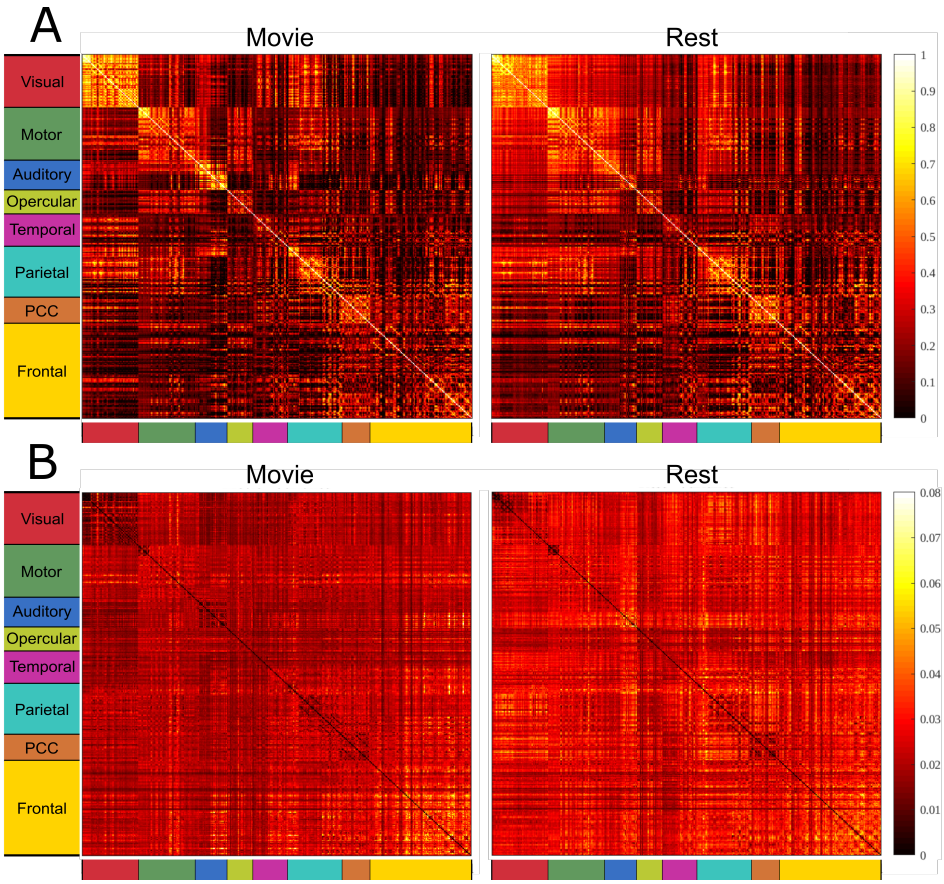

Figure 2.3: (A) Functional connectivity matrices for the movie (left) and resting-state (right) conditions. Connectivity in the movie condition appears to be more modular than that seen in the rest condition. (B) Connectivity variability matrices for the movie (left) and resting-state (right). These matrices demonstrate the magnitude of inter-subject variability at each individual connection.

panel of Figure 2.4.

With widespread increased similarity of functional connectivity across participants in the movie condition, one would expect to see an accompanying widespread reduction of idiosyncratic subject-specific variability. As can be observed in the middle panel of Figure 2.4, that is indeed what was found. Regions with larger proportions of the idiosyncratic component of variance in the resting-state than movie condition were more widespread. This indicates that the movie condition showed reductions in reliably different connectivity across subjects (i.e. reductions in intersubject variability) over multiple scanning sessions when compared to the resting-state condition. Once again, the largest differences were observed in superior and infe-

rior temporal cortex, with large reductions of idiosyncratic variability also observed in medial prefrontal cortex.

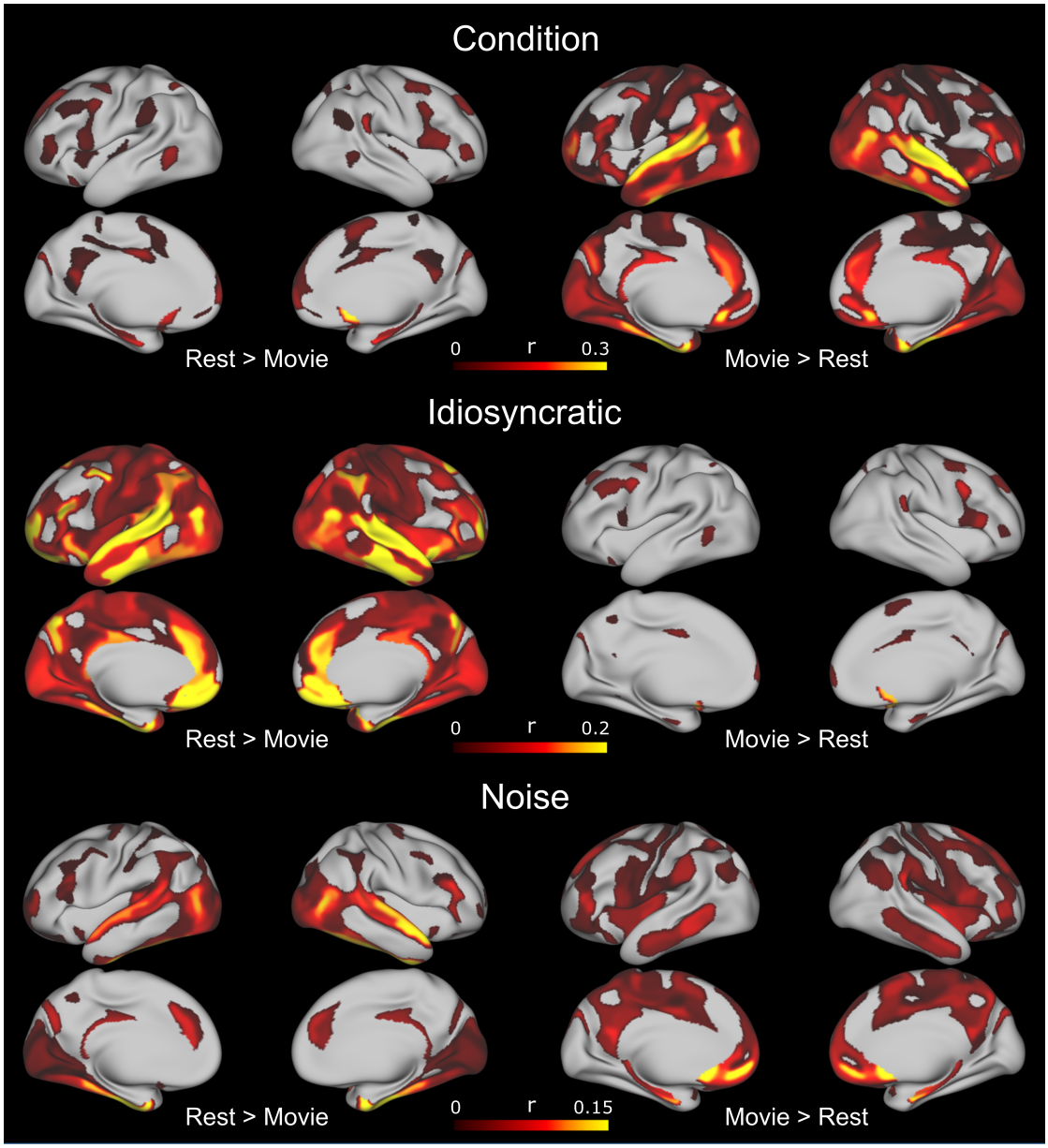

Figure 2.4: Contrast maps displaying regions with unequal contributions to variance of functional connectivity across conditions. Top panel maps show idiosyncratic contribution, middle panel maps show common contribution, and bottom panel maps show noise contribution. Maps in left column show regions where that panel's contribution is higher is the resting-state condition than in the movie condition, and maps in the right column show regions where that panel's contribution is higher in the movie condition than in the resting-state condition.

Differences in noise, representing the reliability of connectivity estimates, were more evenly

balanced across conditions. The trends that can be observed in the bottom panel of Figure 2.4 are reductions of noise in motor and frontal areas in the resting-state condition compared to the movie condition, with the largest difference found in medial prefrontal cortex. The movie resulted in a lower noise component compared to rest in sensory areas, with the largest differences located in superior and inferior temporal cortex. These findings suggest that connectivity in superior and inferior temporal cortex was observed as being more reliable in the movie condition, while connectivity in medial prefrontal cortex was observed as being more reliable in the resting-state condition.

We hypothesized that differences between conditions would be pronounced in visual, auditory, and prefrontal regions. The results of our ANOVA indicate that there was a significant interaction effect between the condition and the model component on the proportion of variance in visual regions, $F(1,51) = 143.37$, $p < 0.001$, in auditory regions, $F(1,29) = 48.86$, $p < 0.001$, and in frontal regions, $F(1,69) = 26.30$, $p < 0.001$. As can be seen in Figure 2.5 the mean idiosyncratic variability was smaller in the movie condition compared to rest in each of the three groupings, while the mean condition variability was larger in the movie condition in each grouping.

Additionally, we performed paired t-tests to investigate the differences in our measure of noise between the two conditions for each of the three groupings. The results indicated that noise was significantly lower in the movie condition for visual cortex, $t(69) = -6.579$, $p < .001$, and auditory cortex, $t(29) = -5.4428$, $p < .001$, but that there was no significant difference between conditions in frontal cortex. Movies result in more reliable connectivity measures across multiple scanning sessions for sensory regions.

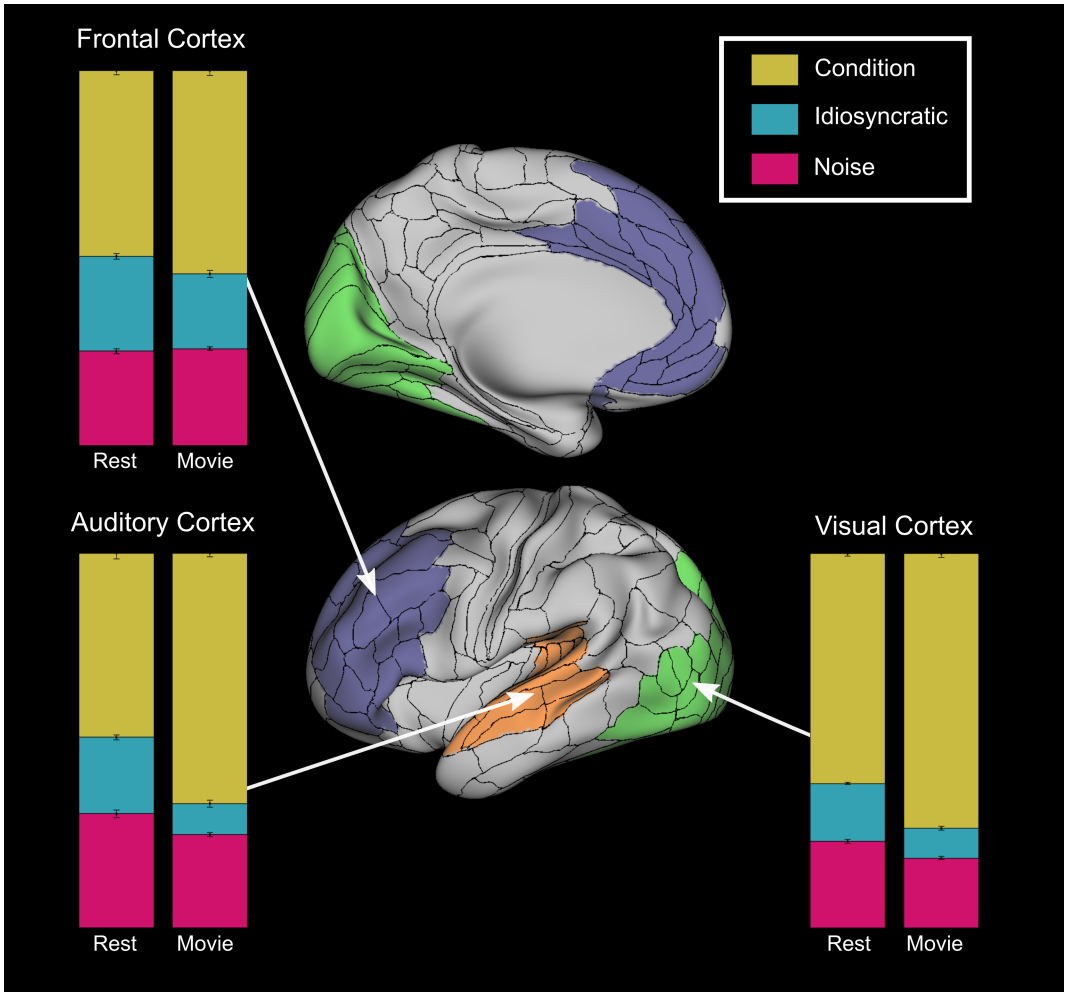

Figure 2.5: Mean functional connectivity contributions grouped into frontoparietal, visual, and auditory cortex. All three areas demonstrate reductions in idiosyncratic functional connectivity. Visual and auditory cortex also show reductions in noise.

2.3.3 Inter-Subject Correlation Overlaps with Differences in Idiosyncratic Variance Between Conditions

ISC values were computed in both the resting-state and movie conditions. Results in the resting-state condition revealed no significant ISC values, as expected [19]. The ISC results in the movie condition can be seen in Figure 2.6. The strongest ISC values were observed in auditory and visual cortex. This is consistent with previous studies of movie-watching fMRI, which demonstrate strong ISC in similar regions, and aligns with what one would expect from an audiovisual stimulus. The analysis also revealed ISC in some frontal regions.

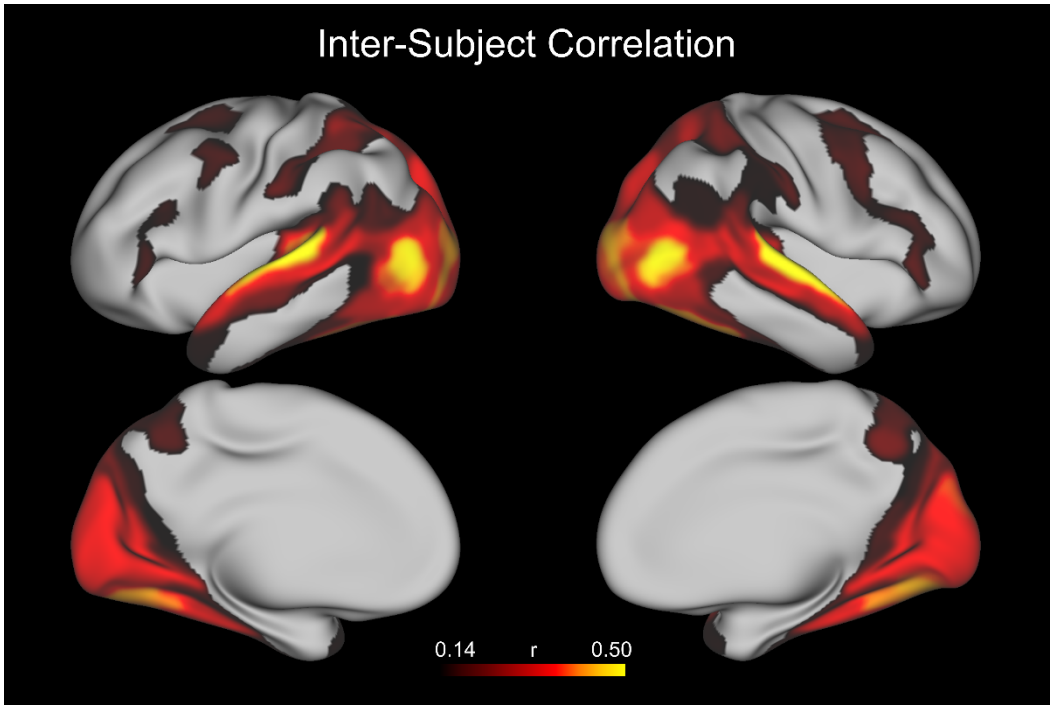

Figure 2.6: Mean ISC over four movie runs. Strongest values of ISC can be found in auditory and visual cortex. Values have been thresholded.

We started by investigating the overlap between the ISC values and the idiosyncratic subject-specific variability seen in the movie condition. This revealed a moderate negative correlation ($r = -0.419$, $p < .001$), indicating that increased synchronization of BOLD activity across participants is related to reductions in idiosyncratic variability of connectivity during movie watching, as expected. We then examined the correlation between the ISC values and the differences in idiosyncratic variability between conditions, revealing a moderate positive correlation ($r = 0.504$, $p < .001$), suggesting that increased synchronization of activity across participants is related to larger differences in idiosyncratic subject-specific variability between conditions. These two findings together imply that the degree of ISC observed in the movie condition is related to the reduction in intersubject variability of functional connectivity.

2.4 Discussion

In this study, we directly compared the intersubject variability of FC in movie watching and resting-state conditions. By modelling intersubject variability in FC as an additive result of condition variability, idiosyncratic subject-specific variability, and noise, we were able to demonstrate that the movie condition results in widespread reductions in intersubject variability of connectivity compared to the rest condition. We also observed more reliable connectivity in visual and auditory regions in the movie condition across multiple scanning sessions. Additionally, we observed a negative relationship between the strength of ISC in the movie condition and the intersubject variability of FC in the movie condition, suggesting synchronization of BOLD activity across participants reflects less variable connectivity across participants, as expected.

The results confirm our initial hypothesis that the movie watching condition results in a widespread reduction in the proportion of idiosyncratic subject-specific variability when compared to the rest condition. One previous study comparing intersubject variability in FC in both conditions found that movie watching resulted in similar magnitudes and a similar spatial distribution of variability as the rest condition [23]. Our analysis is likely more powerful because our sample size is more than double that in [23], with repeated scans and much more scanning time per condition. As a result, our analysis revealed large differences of intersubject variability in visual and auditory regions as well as frontal regions, where variability in the rest condition was higher than in the movie condition. Our findings align with the notion that a more behaviourally constrained scanning paradigm results in less variable FC across the group. This behavioural constraint may reduce variability in cognitive state, arousal, head motion, or any combination of these factors, that have all been shown to affect functional connectivity [34, 35]. In the case of naturalistic stimuli, because the movie synchronizes BOLD activity across subjects in homologous regions, it follows that the correlations between those activity profiles would also be synchronized across subjects.

Reliability of functional connectivity across multiple scanning sessions as measured with the noise component of our model was also higher in the movie condition than in the rest condition. Although resting-state FC measures have shown reliability that is moderate to good across scanning sessions [36, 37], improvements in reliability would contribute to increased sensitivity and enhanced efficacy as a biomarker. Our findings here are consistent with previous work investigating the test-retest reliability of FC metrics in naturalistic stimuli paradigms. In a previous study using the intraclass correlation coefficient, improvements in reliability of FC and graph theory measures of up to 50% were shown across repeated viewings of the same movie when compared to repeated resting-state scans [38]. As with intersubject variability, reliability of FC has also been repeatedly shown to be improved in task conditions when compared to rest, indicating that more behaviourally constrained states lead to lower variability both across subjects and across scanning sessions [39, 40]. The improvements in reliability seen here are restricted to auditory and visual regions, while frontal regions show no significant difference between conditions in the noise component of the model. This may be attributable to different movie clips being shown in each of the four runs, which could lead to differential connectivity in higher order association regions while similarly engaging sensory regions.

Based on the idea that synchronization of BOLD activity across subjects in the movie condition results in lower variability of FC compared to rest, we wanted to investigate the overlap of the ISC map in the movie condition with the idiosyncratic subject-specific variability map in the movie condition. Our results confirm that larger regional ISC values are related to lower proportions of idiosyncratic variability in the movie condition as well as to reductions in idiosyncratic variability in movie fMRI compared to rest. A movie's synchronization effect on the BOLD signal may therefore serve as a marker underlying the observed differences of reduced intersubject variability of FC between conditions. The largest differences in idiosyncratic variability, as well as the largest ISC values, were found in the superior temporal cortex, an area critical for hearing, speech processing, and language [41, 42, 43], each of which are elements involved in the experience of movie watching. ISC maps have been shown to identify

the same foci of activation as GLM analyses [44], so we infer that the time-locked activation of the superior temporal cortex by the movie stimulus may be driving the reductions in variability of connectivity seen across subjects. However, it is evident that the ISC results cannot completely explain these variability reductions, as large differences in idiosyncratic variability were found in the medial prefrontal cortex and inferior temporal cortex without significant ISC. While these differences may suggest a lack of sensitivity of the ISC analysis, they may also suggest that the reductions in variability of connectivity may not be solely caused by elicited activation patterns from the movie stimulus. There could be downstream effects based on synchronization of BOLD activity in areas connecting to a hub region such as the medial prefrontal cortex, a component of the default network which is thought to be involved in global information integration of conscious processing [45, 46].

The results of this study suggest that naturalistic stimuli, and particularly the movie watching condition, leads to less variable estimates of functional connectivity in a young healthy group. Based on the promise of functional connectivity as a biomarker, the implication of this finding is a potential improved sensitivity for the detection of abnormalities in clinical groups. The reduction of clinically irrelevant idiosyncratic variability would, in theory, render clinically relevant changes more apparent. Based on the results in this study, future work is advised in this area, as the results could lead to a translation of these measures to clinical use.

2.4.1 Limitations

A major limitation of this study is the lack of control over the stimuli used in the movie watching condition. The 15-minute movie stimuli employed in the Human Connectome Project made use of short, 2-3 minute clips from independent and blockbuster movies, interleaved with 20 second rest periods. Previous studies have demonstrated the importance of engagement in the stimuli for the observation of strong ISC values, particularly in higher order association areas. We believe that longer and more engaging clips must be used to truly ascertain the degree to

which the movie may reduce variability of FC across subjects. We also believe that repeated presentations of the same clip may be warranted to assess improvements in reliability across scanning sessions. Previous studies have shown that the impact of cognitive engagement on reliability outweighs the potential impact of familiarity due to repeated viewings [38], so the use of the same clip would allow for proper assessment of reliability based on the time-locked nature of the stimulus. A post-hoc analysis comparing reliability the final clip of the movie stimulus, which was the same in each run, to the first 83 seconds of the first clip, which was different across runs, revealed significantly higher reliability in the final clip.

Another limitation relates to the order in which the scans were acquired. The resting-state scans were acquired at the start of each session on four separate days. The movie watching scans were acquired only on days one and four, and the second and fourth runs were acquired after the first and third runs respectively. This poses a concern about differences in fatigue in all of the movie scans because different runs of the movie were acquired at different points in the sessions, and may influence our measure of noise. Issues of session differences are also a concern because runs 2 and 3 of the rest condition were acquired on days when movie watching scans were not acquired. To address these concerns as best as possible, we reanalyzed the data from only runs 1 and 3 of the movie watching condition and runs 1 and 4 of the resting-state condition. This ensured that the data we used were acquired at the same times and on the same days. However, we found that all significant differences between conditions remained, suggesting that fatigue and session differences were not a major source of variability in this data set.

There is also evidence to suggest that the movie watching condition evokes a distinct network structure that is not the same as what is seen in the resting state [47]. Although our results reveal similar global connectivity between the two conditions, we argue here that the movie watching condition provides more stability in relation to functional connectivity estimates across conditions and may increase sensitivity to the detection of clinical abnormalities.

2.5 Conclusion

In this study, we have demonstrated that a movie watching condition leads to widespread reductions in idiosyncratic variability in functional connectivity compared to the resting state conditions in a young healthy group. We confirm that these reductions are related to the strength of ISC elicited by the movie condition, suggesting that the synchronization of BOLD activity across participants can serve as a marker of reduced variability in functional connectivity across participants. Finally, we show that the movie watching condition leads to improvements in reliability of functional connectivity estimates across multiple runs in visual and auditory regions. These findings show that less variable normative estimates of functional connectivity can be obtained in the movie watching condition and may allow for greater sensitivity to clinical abnormalities.

Bibliography

[1] B. Biswal, F. Zerrin Yetkin, V. M. Haughton, and J. S. Hyde, "Functional connectivity in the motor cortex of resting human brain using echo-planar mri," *Magnetic resonance in medicine*, vol. 34, no. 4, pp. 537–541, 1995.

[2] J. D. Power, B. L. Schlaggar, and S. E. Petersen, "Studying brain organization via spontaneous fmri signal," *Neuron*, vol. 84, no. 4, pp. 681–696, 2014.

[3] J. S. Damoiseaux, S. Rombouts, F. Barkhof, P. Scheltens, C. J. Stam, S. M. Smith, and C. F. Beckmann, "Consistent resting-state networks across healthy subjects," *Proceedings of the national academy of sciences*, vol. 103, no. 37, pp. 13848–13853, 2006.

[4] M. W. Cole, D. S. Bassett, J. D. Power, T. S. Braver, and S. E. Petersen, "Intrinsic and task-evoked network architectures of the human brain," *Neuron*, vol. 83, no. 1, pp. 238–251, 2014.

[5] R. M. Hutchison, T. Womelsdorf, J. S. Gati, S. Everling, and R. S. Menon, "Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques," *Human brain mapping*, vol. 34, no. 9, pp. 2154–2177, 2013.

[6] T. O. Laumann, E. M. Gordon, B. Adeyemo, A. Z. Snyder, S. J. Joo, M.-Y. Chen, A. W. Gilmore, K. B. McDermott, S. M. Nelson, N. U. Dosenbach, *et al.*, "Functional system and areal organization of a highly sampled individual human brain," *Neuron*, vol. 87, no. 3, pp. 657–670, 2015.

[7] K. J. Gorgolewski, D. Lurie, S. Urchs, J. A. Kipping, R. C. Craddock, M. P. Milham, D. S. Margulies, and J. Smallwood, "A correspondence between individual differences in the brain's intrinsic functional architecture and the content and form of self-generated thoughts," *PloS one*, vol. 9, no. 5, p. e97176, 2014.

[8] L. Geerligs, M. Rubinov, R. N. Henson, *et al.*, "State and trait components of functional connectivity: individual differences vary with mental state," *Journal of Neuroscience*, vol. 35, no. 41, pp. 13949–13961, 2015.

[9] K. Friston, C. Buechel, G. Fink, J. Morris, E. Rolls, and R. J. Dolan, "Psychophysiological and modulatory interactions in neuroimaging," *Neuroimage*, vol. 6, no. 3, pp. 218–229, 1997.

[10] D. V. Smith, M. Gseir, M. E. Speer, and M. R. Delgado, "Toward a cumulative science of functional integration: a meta-analysis of psychophysiological interactions," *Human brain mapping*, vol. 37, no. 8, pp. 2904–2917, 2016.

[11] E. S. Finn, D. Scheinost, D. M. Finn, X. Shen, X. Papademetris, and R. T. Constable, "Can brain state be manipulated to emphasize individual differences in functional connectivity?," *Neuroimage*, vol. 160, pp. 140–151, 2017.

[12] K. Supekar, V. Menon, D. Rubin, M. Musen, and M. D. Greicius, "Network analysis of intrinsic functional brain connectivity in alzheimer's disease," *PLoS computational biology*, vol. 4, no. 6, p. e1000100, 2008.

[13] A. Lord, D. Horn, M. Breakspear, and M. Walter, "Changes in community structure of resting state functional connectivity in unipolar depression," *PloS one*, vol. 7, no. 8, p. e41282, 2012.

[14] Y. Yu, H. Shen, H. Zhang, L.-L. Zeng, Z. Xue, and D. Hu, "Functional connectivity-based signatures of schizophrenia revealed by multiclass pattern analysis of resting-state fmri from schizophrenic patients and their healthy siblings," *Biomedical engineering online*, vol. 12, no. 1, p. 10, 2013.

[15] A. B. Waites, A. Stanislavsky, D. F. Abbott, and G. D. Jackson, "Effect of prior cognitive state on resting state networks measured with functional connectivity," *Human brain mapping*, vol. 24, no. 1, pp. 59–68, 2005.

[16] A. M. Morcom and P. C. Fletcher, "Does the brain have a baseline? why we should be resisting a rest," *Neuroimage*, vol. 37, no. 4, pp. 1073–1082, 2007.

[17] U. Hasson, Y. Nir, I. Levy, G. Fuhrmann, and R. Malach, "Intersubject synchronization of cortical activity during natural vision," *science*, vol. 303, no. 5664, pp. 1634–1640, 2004.

[18] U. Hasson, R. Malach, and D. J. Heeger, "Reliability of cortical activity during natural stimulation," *Trends in cognitive sciences*, vol. 14, no. 1, pp. 40–48, 2010.

[19] L. Naci, R. Cusack, M. Anello, and A. M. Owen, "A common neural code for similar conscious experiences in different individuals," *Proceedings of the National Academy of Sciences*, vol. 111, no. 39, pp. 14277–14282, 2014.

[20] M. F. Glasser, S. M. Smith, D. S. Marcus, J. L. Andersson, E. J. Auerbach, T. E. Behrens, T. S. Coalson, M. P. Harms, M. Jenkinson, S. Moeller, *et al.*, "The human connectome project's neuroimaging approach," *Nature neuroscience*, vol. 19, no. 9, p. 1175, 2016.

[21] E. Simony, C. J. Honey, J. Chen, O. Lositsky, Y. Yeshurun, A. Wiesel, and U. Hasson, "Dynamic reconfiguration of the default mode network during narrative comprehension," *Nature communications*, vol. 7, p. 12141, 2016.

[22] D. Kim, K. Kay, G. L. Shulman, and M. Corbetta, "A new modular brain organization of the bold signal during natural vision," *Cerebral Cortex*, vol. 28, no. 9, pp. 3065–3081, 2017.

[23] T. Vanderwal, J. Eilbott, E. S. Finn, R. C. Craddock, A. Turnbull, and F. X. Castellanos, "Individual differences in functional connectivity during naturalistic viewing conditions," *Neuroimage*, vol. 157, pp. 521–530, 2017.

[24] S. Mueller, D. Wang, M. D. Fox, B. T. Yeo, J. Sepulcre, M. R. Sabuncu, R. Shafee, J. Lu, and H. Liu, "Individual variability in functional connectivity architecture of the human brain," *Neuron*, vol. 77, no. 3, pp. 586–595, 2013.

[25] J. S. Anderson, M. A. Ferguson, M. Lopez-Larson, and D. Yurgelun-Todd, "Reproducibility of single-subject functional connectivity measurements," *American journal of neuroradiology*, vol. 32, no. 3, pp. 548–555, 2011.

[26] D. C. Van Essen, S. M. Smith, D. M. Barch, T. E. Behrens, E. Yacoub, K. Ugurbil, W.-M. H. Consortium, *et al.*, "The wu-minn human connectome project: an overview," *Neuroimage*, vol. 80, pp. 62–79, 2013.

[27] A. T. Vu, K. Jamison, M. F. Glasser, S. M. Smith, T. Coalson, S. Moeller, E. J. Auerbach, K. Uğurbil, and E. Yacoub, "Tradeoffs in pushing the spatial resolution of fmri for the 7t human connectome project," *Neuroimage*, vol. 154, pp. 23–32, 2017.

[28] K. Uğurbil, J. Xu, E. J. Auerbach, S. Moeller, A. T. Vu, J. M. Duarte-Carvajalino, C. Lenglet, X. Wu, S. Schmitter, P. F. Van de Moortele, *et al.*, "Pushing spatial and temporal resolution for functional and diffusion mri in the human connectome project," *Neuroimage*, vol. 80, pp. 80–104, 2013.

[29] M. F. Glasser, S. N. Sotiropoulos, J. A. Wilson, T. S. Coalson, B. Fischl, J. L. Andersson, J. Xu, S. Jbabdi, M. Webster, J. R. Polimeni, *et al.*, "The minimal preprocessing pipelines for the human connectome project," *Neuroimage*, vol. 80, pp. 105–124, 2013.

[30] M. F. Glasser, T. S. Coalson, E. C. Robinson, C. D. Hacker, J. Harwell, E. Yacoub, K. Ugurbil, J. Andersson, C. F. Beckmann, M. Jenkinson, *et al.*, "A multi-modal parcellation of human cerebral cortex," *Nature*, vol. 536, no. 7615, p. 171, 2016.

[31] D. C. Van Essen, M. F. Glasser, D. L. Dierker, J. Harwell, and T. Coalson, "Parcellations and hemispheric asymmetries of human cerebral cortex analyzed on surface-based atlases," *Cerebral cortex*, vol. 22, no. 10, pp. 2241–2262, 2011.

[32] Y. Ren, V. T. Nguyen, L. Guo, and C. C. Guo, "Inter-subject functional correlation reveal a hierarchical organization of extrinsic and intrinsic systems in the brain," *Scientific reports*, vol. 7, no. 1, p. 10876, 2017.

[33] G. Chen, Y.-W. Shin, P. A. Taylor, D. R. Glen, R. C. Reynolds, R. B. Israel, and R. W. Cox, "Untangling the relatedness among correlations, part i: nonparametric approaches to inter-subject correlation analysis at the group level," *Neuroimage*, vol. 142, pp. 248–259, 2016.

[34] D. Stoffers, B. A. Diaz, G. Chen, A. den Braber, D. van't Ent, D. I. Boomsma, H. D. Mansvelder, E. de Geus, E. J. Van Someren, and K. Linkenkaer-Hansen, "Resting-state fmri functional connectivity is associated with sleepiness, imagery, and discontinuity of mind," *PloS one*, vol. 10, no. 11, p. e0142014, 2015.

[35] T. T. Liu, "Noise contributions to the fmri signal: an overview," *NeuroImage*, vol. 143, pp. 141–151, 2016.

[36] C. C. Guo, F. Kurth, J. Zhou, E. A. Mayer, S. B. Eickhoff, J. H. Kramer, and W. W. Seeley, "One-year test–retest reliability of intrinsic connectivity network fmri in older adults," *Neuroimage*, vol. 61, no. 4, pp. 1471–1483, 2012.

[37] U. Braun, M. M. Plichta, C. Esslinger, C. Sauer, L. Haddad, O. Grimm, D. Mier, S. Mohnke, A. Heinz, S. Erk, *et al.*, "Test–retest reliability of resting-state connectivity network characteristics using fmri and graph theoretical measures," *Neuroimage*, vol. 59, no. 2, pp. 1404–1412, 2012.

[38] J. Wang, Y. Ren, X. Hu, V. T. Nguyen, L. Guo, J. Han, and C. C. Guo, "Test–retest reliability of functional connectivity networks during naturalistic fmri paradigms," *Human brain mapping*, vol. 38, no. 4, pp. 2226–2241, 2017.

[39] K. Specht, K. Willmes, N. J. Shah, and L. Jäncke, "Assessment of reliability in functional imaging studies," *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 17, no. 4, pp. 463–471, 2003.

[40] H. Cao, M. M. Plichta, A. Schäfer, L. Haddad, O. Grimm, M. Schneider, C. Esslinger, P. Kirsch, A. Meyer-Lindenberg, and H. Tost, "Test–retest reliability of fmri-based graph theoretical properties during working memory, emotion processing, and resting state," *Neuroimage*, vol. 84, pp. 888–900, 2014.

[41] M. A. Howard, I. Volkov, R. Mirsky, P. Garell, M. Noh, M. Granner, H. Damasio, M. Steinschneider, R. Reale, J. Hind, *et al.*, "Auditory cortex on the human posterior superior temporal gyrus," *Journal of Comparative Neurology*, vol. 416, no. 1, pp. 79–92, 2000.

[42] R. C. Martin, "Language processing: functional organization and neuroanatomical basis," *Annual review of psychology*, vol. 54, no. 1, pp. 55–89, 2003.

[43] M. A. Gernsbacher and M. P. Kaschak, "Neuroimaging studies of language production and comprehension," *Annual review of psychology*, vol. 54, no. 1, pp. 91–114, 2003.

[44] J. Pajula, J.-P. Kauppi, and J. Tohka, "Inter-subject correlation in fmri: method validation against stimulus-model based analysis," *PloS one*, vol. 7, no. 8, p. e41196, 2012.

[45] R. L. Buckner, J. Sepulcre, T. Talukdar, F. M. Krienen, H. Liu, T. Hedden, J. R. Andrews-Hanna, R. A. Sperling, and K. A. Johnson, "Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to alzheimer's disease," *Journal of neuroscience*, vol. 29, no. 6, pp. 1860–1873, 2009.

[46] D. Vatansever, D. K. Menon, A. E. Manktelow, B. J. Sahakian, and E. A. Stamatakis, "Default mode dynamics for global functional integration," *Journal of Neuroscience*, vol. 35, no. 46, pp. 15254–15262, 2015.

[47] K. L. Bottenhorn, J. S. Flannery, E. R. Boeving, M. C. Riedel, S. B. Eickhoff, M. T. Sutherland, and A. R. Laird, "Cooperating yet distinct brain networks engaged during naturalistic paradigms: A meta-analysis of functional mri results," *Network Neuroscience*, vol. 3, no. 1, pp. 27–48, 2018.

Chapter 3

Conclusion

The purpose of this thesis was to explore the differences in intersubject variability of functional connectivity in resting-state and movie-watching fMRI. In chapter 1, I introduced both paradigms and discussed the potential use of functional connectivity measures for clinical purposes, including as biomarkers. Because functional connectivity has been primarily explored in the resting-state condition, I outlined potential disadvantages in resting-state which may be addressed by the movie-watching condition. Movies reduce head motion, improve wakefulness, and may reduce variability in cognitive states across the group, all of which would decrease clinically irrelevant sources of variability in measures of functional connectivity. However, a comprehensive direct comparison of intersubject variability between the two fMRI paradigms has yet to be performed.

In chapter 2, I attempted to address this gap in the literature by investigating intersubject variability of functional connectivity in a healthy group in both a resting-state and movie-watching fMRI condition. By dividing variability into three components, we attempted to isolate idiosyncratic subject-specific sources of variability, by controlling for the effects of intrasubject variability and condition variability. The results demonstrated widespread reductions in idiosyncratic subject-specific variability in the movie-watching condition when compared to the resting-state condition. These differences in variability of functional connectivity were significant in both sensory regions as well as frontal regions, responsible for higher-order

functioning. Decreased intrasubject variability of functional connectivity was also observed in sensory regions for the movie condition compared to rest, indicating that functional connectivity measures were more reliable across multiple scanning sessions during movie watching. Finally, we observed that synchronization of BOLD activity across subjects was related to the magnitude of differences that were observed in intersubject variability of functional connectivity between conditions. This indicates that the synchronizing effects that the movie has on BOLD activity may also lead to a synchronization of functional connectivity across subjects.

Given the results of this study, we hope that naturalistic stimuli, in particular movie watching, are considered in future studies investigating clinical differences in functional connectivity. Up to this point, the resting-state paradigm has been the primary technique used to study functional connectivity in both healthy and clinical groups. We believe that movie watching offers improvements in data quality, through the reduction of head motion and improvements in participant wakefulness, and enforces behavioural constraints for studying global functional connectivity. These behavioural constraints appear to reduce idiosyncratic variability in similar healthy subjects, which, in theory, would improve sensitivity to clinically relevant differences in functional connectivity. Early work in our lab has already demonstrated that movie watching can reveal functional connectivity differences in an epilepsy group. However future work must validate these findings so that clinical translation of these measures can be accelerated.

Appendix A

Model

In this study we model functional connectivity as:

$$y = \alpha + \beta_j + \epsilon_j s \tag{A.1}$$

where:

y = functional connectivity
α = connectivity that is common across the group
β_{j} = connectivity that is idiosyncratic to subject j
ϵ_{js} = noise for subject j and session s

We assume that all components of the model are independent from one another.

The correlation coefficient is obtained through Equation A.2.

$$r_{X,Y} = \frac{cov(X, Y)}{\sigma_X \sigma_Y} \tag{A.2}$$

where:

cov = covariance
σ_{X} = Standard deviation of X
σ_{Y} = Standard deviation of Y

Here, X and Y are connectivity fingerprints (i.e. 359 element array where each value represents the strength of connectivity between one region and every other region of the parcellation). In this model, we assume that total variance in each correlation map for each subject or session is the same, therefore:

$$\sigma_X = \sigma_Y \tag{A.3}$$

making the equation for the correlation coefficient,

$$r_{X,Y} = \frac{cov(X,Y)}{\sigma^2_T} \tag{A.4}$$

where:

$\sigma^2{}_{\mathrm{T}}$ = Total variance

The variance of the model components in Equation A.1 can be found through two correlations.

First, the α variance can be estimated based on a correlation between the connectivity fingerprints of two different subjects. Let X_1 be the connectivity fingerprint for subject X in scanning session 1, and let Y_1 be the connectivity fingerprint for subject Y in scanning session 1.

$$r_{X_1,Y_1} = \frac{covX_1, Y_1}{\sigma^2_T}$$

$$r_{X_1,Y_1} = \frac{cov(\alpha + \beta_X + \epsilon_{X1}, \alpha + \beta_Y + \epsilon_{Y1})}{\sigma^2_T}$$

$$r_{X_1,Y_1} = \frac{1}{\sigma^2_T} * (var(\alpha) + cov(\alpha,\beta_Y) + cov(\alpha,\epsilon_{Y1}) + cov(\beta_X,\alpha) + cov(\beta_X,\beta_Y) + cov(\beta_X,\epsilon_{Y1}) + cov(\epsilon_{X1},\alpha) + cov(\epsilon_{X1},\beta_Y) + cov(\epsilon_{X1},\epsilon_{Y1}))$$

$$r_{X_1,Y_1} = \frac{var(\alpha) + 0 + 0 + 0 + 0 + 0 + 0 + 0 + 0}{\sigma^2_T}$$

$$r_{X_1,Y_1} = \frac{\sigma^2_\alpha}{\sigma^2_T}$$

Because the model components are independent, and the covariance of independent variables in 0, the correlation equation reduces to the variance of α over the total variance.

Second, the ϵ variance can be estimated based on a correlation between connectivity fingerprints from the same subject in two different sessions. Let X_1 be the connectivity fingerprint for subject X in scanning session 1, and let X_2 be the connectivity fingerprint for subject X in scanning session 2.

$$r_{X_1,X_2} = \frac{cov(X_1, X_2)}{\sigma_T^2}$$

$$r_{X_1,X_2} = \frac{cov(\alpha + \beta_X + \epsilon_{X1}, \alpha + \beta_X + \epsilon_{X2})}{\sigma_T^2}$$

$$r_{X_1,X_2} = \frac{1}{\sigma_T^2} * (var(\alpha) + cov(\alpha, \beta_X) + cov(\alpha, \epsilon_{X2}) + cov(\beta_X, \alpha) + var(\beta_X) + cov(\beta_X, \epsilon_{X2}) + cov(\epsilon_{X1}, \alpha) + cov(\epsilon_{X1}, \beta_X) + cov(\epsilon_{X1}, \epsilon_{X2}))$$

$$r_{X_1,X_2} = \frac{var(\alpha) + var(\beta_X) + 0 + 0 + 0 + 0 + 0 + 0 + 0}{\sigma_T^2}$$

$$r_{X_1,X_2} = \frac{\sigma_\alpha^2 + \sigma_{\beta_X}^2}{\sigma_T^2}$$

Because the total variance is simply the sum of variances from each component of the model, we can take the complement of the result from the above correlation to obtain and estimate of the variance.

$$1 - r_{X_1,Y_1} = \frac{\sigma_\alpha^2 + \sigma_{\beta_X}^2 + \sigma_\epsilon^2}{\sigma_\alpha^2 + \sigma_{\beta_X}^2 + \sigma_\epsilon^2} - \frac{\sigma_\alpha^2 + \sigma_{\beta_X}^2}{\sigma_\alpha^2 + \sigma_{\beta_X}^2 + \sigma_\epsilon^2} = \frac{\sigma_\epsilon^2}{\sigma_\alpha^2 + \sigma_{\beta_X}^2 + \sigma_\epsilon^2} = \frac{\sigma_\epsilon^2}{\sigma_T^2}$$

Finally, to obtain an estimate of the variance of β we find the difference between the complements of r_{X_1,X_2} and r_{X_1,Y_1}.

$$1 - r_{X_1,X_2} = \frac{\sigma_\epsilon^2}{\sigma_T^2}$$

$$1 - r_{X_1,Y_1} = \frac{\sigma_\beta^2 + \sigma_\epsilon^2}{\sigma_T^2}$$

$$(1 - r_{X_1,Y_1}) - (1 - r_{X_1,X_2}) = \frac{\sigma_\beta^2 + \sigma_\epsilon^2}{\sigma_T^2} - \frac{\sigma_\epsilon^2}{\sigma_T^2} = \frac{\sigma_\beta^2}{\sigma_T^2}$$

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Research Abstracts:

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O'Reilly, M., Khan, A.R., Johnsrude, I. Stability of Functional Networks in Resting State and Movie Stimulation Conditions. 2018 Sixth Biennial Conference on Resting-State and Brain Connectivity. September 24-29. Montreal, Quebec, Canada.

O'Reilly, M., Khan, A.R., Johnsrude, I. Stability of Functional Networks in Resting State and Movie Stimulation Conditions. 2018 Robarts Research Retreat. June 1. London, Ontario, Canada.